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EDUCATION IN MOTOR VEHICLE ACCIDENT PREVENTION

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I WOULD LIKE to start my discussion with an appropriate quotation from the yearbook "Safety Education" prepared in 1940 by the American Association of School Administrators: "It is to the school particularly that we must look for the development of the knowledge, the attitudes, the habits, and the skills that are necessary if we are to live with reasonable safety in the modern world."

This quotation, I think, is especially appropriate at this time when we are putting renewed emphasis on education as a result of the launching of satellites by Russia and the United States. It is even more significant and important today—18 years later—than it was when originally prepared, for the entire world looks to education for guidance and direction.

However, since Russia and the United States launched their satellites, those of us in the field of education and especially those of us teaching courses in driver education will be severely criticized for participating in a program considered by many to be a frill. The emphasis for many months to come will be on science courses, and the elimination of home economics, shop, health and physical education, driver education, and other similar courses suddenly considered nonessential in this space age will be at least debated if not accomplished.

Too many leading educators, through ignorance, misinformation, or inertia, consider driver education a frill and would like to see it dropped completely. Evidence shows that youths trained in driving education programs while in high school have 40 to 66% fewer violations and accidents than similar groups not so trained. Now is the time for the physician to become a real crusader for one of the most important of our school subjects—driver education—that is, if it is believed that education should be preparation for living.

Frankly, I feel that people are emotional and are not using their heads when orating and writing about the present "needs" in education. I also believe that the main reason for the present-day cry to eliminate driver education is the fact that many Americans have little knowledge of the urgency, objectives, scope, and results of the high school driver education program.

Both former President Truman and President Eisenhower have publicly stated that traffic accidents form a major problem in the United States and have called five President's Highway Safety

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Read in the Symposium and Panel Discussion on Motor Vehicle Accidents and their Prevention in the Session on Traffic Accidents before the Section on Miscellaneous topics at the 107th Annual Meeting of the American Medical Association, San Francisco, June 25, 1958.

Conferences to do something about the situation. Killing 40,000 and injuring a million and a half annually is nothing less than an indictment against this great nation. Since the advent of the motor car, over 1,200,000 citizens have been killed, to say nothing of the milions seriously injured and the billions of dollars lost in property damages.

We now have evidence that youths trained in high school have 40 to 66% fewer violations and accidents than similar groups not so trained. This is ample evidence of the value of these courses and the need to extend them. And, further, think of the training in that important field of science in which chemical tests for intoxication, friction, centrifugal force, kinetic energy, gravity, motion, power, heat, light, color, and sound are discussed during the course.

We believe it is extremely shortsighted to feverishly teach many young scientists how to travel to the moon when, through lack of training in how to travel on this earth, their lives will be snuffed out completely or they will be turned into hopeless cripples before they have a chance to put their space travel knowledge to use.

We look to the educators to prepare youth for living now as well as in the future. Rather than eliminate learning in earth travel, let us increase it until every boy and every girl of legal driving age will be able to receive this instruction and driver education will assume its rightful role of importance in this age when the motor car is still very much with us. Let us cease to consider this area of education as a mere frill.

In spite of the present criticism, driver education is on the move both forward and "for good." The following progress report will serve as a basis for this statement.

Progress in Driver Education Programs

This year we are celebrating our 25th year in high school driver education. This new subject has stood the criticism, the growing pains, and everything else for a quarter of a century. The program progressed from one high school offering driver education during the 1933-1934 school term to 11,846 high schools during the 1957-1958 school term and from 20 students enrolled in that first course at State College, Pennsylvania, High School to 1,219,065 enrolled in the 1957-1958 courses. This is ample evidence that driver education is on the move and that this relatively new teaching field has the look of permanence.

Teacher Preparation.—There are over 800 college professors prepared to offer safety education courses for teachers of every grade level. This is real progress when we look back to 1937 when the first college professors' seminar in driver education was offered at the University of Kentucky.

There are over 18,000 high school teachers prepared to offer driver education courses. During the 1957-1958 school term, 453 colleges and universities offered 929 courses in safety education. This also is real progress when we look back to the summer of 1936 when Pennsylvania State University offered the first course for high school teachers in driver education.

In 1947, the State Council on Education in Pennsylvania established 12 semester hours of credit in safety education as the teacher certification requirement to teach driver education in Pennsylvania high schools. In addition, each teacher must hold a valid teaching certificate. Many of the states require the valid teaching certificate and two courses in the field of safety, one in general safety education and one in driver education. A few of the states require only a valid teaching certificate.

Organizational Programs.—Six states received the United States' top award in this field, the achievement award for the extent and quality of driver education programs conducted during the 1957-1958 school year. Six earned the progress award. This award program is conducted each year by the Association of Casualty and Surety Companies.

In 1938, when Dr. Charles Glenn was President of the American Association of School Administrators, it was decided to have a yearbook on the subject "Safety Education." Dr. Henry H. Hill was appointed chairman of the commission, and with the direction of a group of educators and safety specialists the book was released in 1940. This particular book gave visible evidence that educators were interested in safety education.

Another milestone in the development of the safety education program on a national basis was the establishment in 1943 of the National Commission on Safety Education, a division of the National Education Association (NEA). This commission gave prestige and status to the entire safety movement. Funds were made available in 1944 for the operation of the commission.

In 1949, the first conference of the new Pennsylvania Association for Safety Education (PASE) was held at Hershey, Pa. There are now close to 400 members of this association. The annual meeting offers both college and high school instructors an opportunity to exchange ideas and improve teaching methods. There are now 40 such state associations.

The presidents of the state associations met in Washington, D. C., in 1956 and formed the American Driver and Safety Education Association. The first conference was held in Philadelphia in 1957 in connection with the NEA centennial. The second conference was held at the University of Colorado, June 22-24, 1958. These conferences help the teachers improve their teaching in both the classroom and the practice driving part of the program.

The National Commission on Safety Education has arranged for three national driver education conferences. The first was at Jackson's Mill in 1949, the second at Michigan State University in 1953, and the third at Purdue University in 1958.

These national conferences are responsible for the administrative practices and policies used in driver education courses today. Thirty clock hours in the classroom and a minimum of six clock hours in practice driving for each student are standards recommended by the national conference.

Contributions.—During the 1957-1958 school term, the automobile dealers lent over 11,000 cars to schools at a value of over 24 million dollars. This is truly a significant civic activity on the part of the dealers.

Fifteen states now offer financial aid to schools when their driver education courses meet accepted standards. Bills will be introduced by other states, and in all probability 50% of the states will offer financial aid within the next five years. The details of the present plan are available from the American Automobile Association and the National Commission on Safety Education.

Teaching Techniques

The college instructors in Pennsylvania meet every year during the PASE conference to discuss ways and means to improve the safety education courses on the college level. In addition, they meet for two days in September to improve teaching materials and methods. California and Michigan also hold conferences regularly to bring the college professors together in an effort to improve their safety education courses.

Youth Driver Education.—The young people today are just as eager and anxious as adults to help solve some of the serious problems of the United States. One method that is being used successfully in the field of traffic is the holding of youth conferences; others include radio and television panels. These young people need the assistance of the driver education teachers in arranging facilities, transportation, discussion topics, speakers, and method of conducting such conferences.

For a number of years the Junior Chamber of Commerce has been sponsoring Teen-Age Road-e-os. In addition, many local areas conduct their own "road-e-os." If you cooperate in such an activity, you should make sure that every step is taken to make it of high quality. In our community, for instance, a road test is given as well as skill tests and a written test. These tests are administered by professionals in the field.

Economy Runs.—The economy run is gaining in popularity all over the nation. In most places it is conducted under the sponsorship of one oil company. However, in some places it is conducted with the cooperation of a number of oil companies and other organizations.

Adult Driver Education.—Each year over a million adults complete courses in driver education conducted by colleges, high schools, police departments, American Automobile Association clubs, commercial driving schools, motor vehicle fleets, and others. In a number of instances, the adult driver education schools are licensed by the state. Pennsylvania's commercial schools are under the supervision of the Department of Public Instruction. One of the outstanding schools for training commercial drivers is at North Carolina State College. The graduates have established an enviable record.

The Common Carrier Conference of the American Trucking Associations, Inc., is making plans to have vocational schools conduct courses for commercial drivers. This is now being done at Washington High School in Los Angeles.

The National Committee for Motor Fleet Supervisor Training, working cooperatively with over 50 colleges and universities, has prepared over 15,000 supervisors who have under their direction over 2 million drivers. Another forward move is the directive from Air Force Headquarters in Washington, D. C., requiring every airman 25 years of age and under to complete 10 hours of instruction in driver education. These different programs are certainly indications that driver education is on the move.

Driver Licensing and Preparation.—In Connecticut and Michigan, laws have been passed requiring boys and girls to complete in a satisfactory manner an approved course in driver education in order to get a license at 16 or 17 years of age. There is also considerable agitation for more junior license laws which would require approved courses and would permit driving only at certain hours without adult supervision.

There are a number of states that now permit boys and girls to practice in the school car with the approved instructors six months or a year before the age at which a license can be obtained. According to reports from the instructors, preference is given to the six-month period because there is too long a gap in a year's interval between course completion and the examination for a license.

Teachers, in general, do a fairly good job when conducting their driver education courses. However, there is always plenty of room for improvement. One of the big problems is the cost for the practice driving part of the program. Efforts are being made to cut this cost. One method is to use simulators, such as the American Automobile Association Auto Trainer or the Aetna Drivotrainer. Those who have made studies of the use of these devices say that they reduce significantly the amount of practice time. Some experiments showed that pupils with 12 hours practice first in a simulator reduced the actual behind-the-wheel time from six to three hours. Of course, we must consider equipment costs and the cost of the space for the simulators. But, in the long run, the cost per pupil should be less.

Other plans to help with the practice driving have included use of cadet teachers, high school seniors, and school bus drivers. In most instances

these plans are not very satisfactory because such persons are not professional teachers. Some instructors use flash film, commentary driving, or the discussion-decision technique to improve driving practice experience and to shorten time and costs.

In Michigan, the multiple-car plan is used quite extensively for the practice driving part of the program. One instructor, through the use of a public address system, or car radios, can handle from 6 to 12 cars on the driving range. The driving range usually includes signs, signals, markings, one-way streets, curves, parking stalls, and other traffic patterns found in regular driving.

It is quite evident from these different plans that a variety of approaches are being used to reduce the cost of the program and still produce good drivers.

Supervisors in Safety Education.—Twenty-five years ago we could have counted on the fingers of one hand the number of cities and states having a full-time supervisor in safety education. Today, practically every city and community, as well as every state, has at least one individual assigned full time or part time to safety education in the school system. In some instances, there is a full time staff worker in driver education alone. When this is the case, the program has acceptance by top educators.

Scientific Advancement

We are all aware of the research dealing with seat belts and harness, padded instrument panels, recessed steering posts, padded sunvisors, shatterproof glass in rear-view mirrors, special door latches, rearward seating, and, finally, the safety car with the driver in the middle and without a steering wheel. Such developments will most certainly affect our teaching.

We also know that it is now possible to keep a car in its own lane automatically and to warn drivers of impending dangers, such as curves and fog, electronically. Research in these fields will continue because of the help such installations will offer in reducing traffic accidents.

Conclusions

One of the big problems in driver education today is getting the acceptance and approval of top educators. Too many leading educators, through ignorance, misinformation, or inertia, still consider driver education a frill and would like to see it dropped completely. Others advocate its being scheduled as a vocational subject or conducted during the suggested 13th year in the public schools.

I believe such problems help us because we are now forced to stand up and speak out just as positively in favor of driver education as others are speaking negatively about this program. Please let your voice be heard in public. Now is the time to become a real crusader for one of the most important of our school subjects—driver education—that is, if you believe that education should be the preparation for living. We are counting on your help, not only as citizens and parents but as a group of people welded into one of the most effective of all organizations for combating human misery—the medical profession. We enlist your aid.

I would like to close with this basic concept concerning traffic, one that offers great hope in reducing the all-too familiar traffic accidents: Our greatest potential for achieving smooth, safe, orderly, and efficient movement of traffic is through a driver education program in every high school that reaches every boy and girl prior to the time when they become legally old enough to be licensed to drive.

This, then, is the long-range program that will eventually offer the greatest contribution to the development of good traffic citizenship. It doesn't cost to teach them to drive—it pays.

CHOLESTEROL PRESENT IN ALL CELLS.—Cholesterol is an alicyclic unsaturated alcohol present in all animal cells and in blood. It is the characteristic sterol of animals, the plant sterols having additional carbon in the side-chain. In the body, cholesterol functions as a precursor of the bile acids and of numerous hormones of the adrenals and gonads. Cholesterol itself is a constituent of lipoproteins and both in serum or in tissues may occur either free or esterified by fatty acids. . . . As well as being absorbed from food, cholesterol is synthesized in the animal body, as was shown quite early by feeding experiments. The liver is an important site of synthesis and appears to be the principal endogenous source of the cholesterol in blood plasma. Many other tissues are also known to synthesize the sterol: the intestinal mucosa, ovary, and all foetal tissues of the rabbit; the theca interna, theca externa, and zona granulosa of the hen's ovary; the adrenal cortex, kidney, the testis and skin are all sites of active synthesis.—J. W. Cornforth, M.Sc., D.Phil., F.R.S., and G. Popjak, M.D., F.R.IC, Biosynthesis of Cholesterol, *British Medical Bulletin*, September, 1958

THROMBOPENIC PURPURA AS A COMPLICATION OF MUMPS

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Thrombopenic purpura and nonthrombopenic purpura are occasionally observed in patients with infectious diseases. Clement and Diamond [1] reported on the findings in 96 children with thrombopenic purpura. In 65 of these children the purpura was associated mostly with upper respiratory infections, but it occurred also as a complication of rubella, chickenpox (varicella), and infectious mononucleosis.

We are presenting the clinical course of three adults with mumps who had thrombopenic purpura as a serious complication. In reviewing the literature, we have been unable to find any documented instance of this complication occurring with mumps. Perhaps thrombopenic purpura appears more frequently in mumps than is realized, since the three patients were seen over a relatively brief period of time. Further emphasis should be given to this complication because of the difficulties encountered in controlling the bleeding.

Three adults with mumps had thrombopenic purpura as a serious sequela. Thrombopenia must be added to orchitis and meningoencephalitis as a complication of this not uncommon infection in adults. Although direct invasion of the tissues by virus may be responsible for the inflammatory reaction, the possibility also exists that a state of acquired hypersensitivity may be the cause. Steroid therapy is helpful in thrombopenia occurring as a complication of mumps.

Report of Cases

Case 1.—A 65-year-old woman entered the University Hospitals on March 7, 1955, because of bleeding. Having always enjoyed good health, the patient developed an occipital headache six weeks prior to admission. A week later parotid swelling appeared, which was soon followed by epistaxis and "red spots all over the body." Within the next few weeks, lethargy was associated with vaginal bleeding, hematuria, and ecchymoses.

Her only medicaments were salicylates and an iron preparation. Of considerable significance was the fact that just prior to her illness she had had close contact with several members of her family, including children, who had mumps. She was not certain of having had mumps previously. There was no history of a bleeding tendency. Her family history was irrelevant.

Physical examination revealed an obese woman with a normal temperature and pulse rate and a blood pressure of 165/85 mm. Hg. There was a fresh hemorrhage in the left ocular fundus. A grade 2 systolic murmur was heard over the precordium. The liver and spleen were not palpable. There was a generalized petechial eruption of the skin over the entire body, especially the legs.

The pertinent laboratory data revealed 3+ erythrocytes in the urine. Hematological data showed a hemoglobin level of 14.0 Gm. %, erythrocytes, 4,210,000 per cubic millimeter, leukocytes, 5,800 per cubic millimeter with 68% neutrophils, 27% lymphocytes, and 5% monocytes, platelets, 18,000 per cubic millimeter, a bleeding time greater than 15 minutes, and a clotting time of 5 minutes, with only a slight retraction of the clot in 17 hours. The prothrombin time was normal. The cuff test gave positive results. The reticulocyte count was 4.9%, and a section of sternal bone marrow showed a marked increase in megakaryocytes. Findings on the direct and indirect Coombs' test were negative. The four-day fecal urobilinogen excretion was normal. The complement-fixation test for mumps showed positive results in a dilution of 1:64. The L.E. cell test was negative. Liver function tests were normal except for a 3+ cephalin flocculation.

Because of the diffuse bleeding and the scarcity of peripheral platelets, she was given 200 mg. of cortisone orally for the first three days. No improvement occurred, and for the three following days 400 mg. of cortisone was administered daily. The daily intake of cortisone was then reduced to 300 mg. Because only 18,000 platelets per cubic millimeter were present and because of continued hemorrhage, splenectomy was carried out on March 18, 1955, after preparation with one unit of whole blood. The resected spleen weighed 180 Gm. and appeared normal, grossly and histologically. Cortisone therapy was continued. Two days after operation the platelets numbered 144,000 per cubic millimeter. The cortisone intake was reduced to 150 mg. daily on March 23, at which time there were 371,000 platelets and 18,000 leukocytes per cubic millimeter. The dose of cortisone was gradually reduced, and this therapy was discontinued on March 25, at which time 15 units of ACTH was administered. At this point there were 765,000 platelets per cubic millimeter. The platelet level then gradually stabilized at 90,000 to 100,000 per cubic millimeter. She was discharged from the hospital on April 6, 1955, after an uncomplicated postoperative period. She has had good health up through the last follow-up examination on June 10, 1958.

Comment.—This elderly woman undoubtedly had mumps with thrombopenic purpura as a complication. The number of platelets remained low through the period of steroid therapy, and splenectomy was followed by only a transient rise in the platelet level.

Case 2.—A 27-year-old woman was admitted to the University Hospitals on March 13, 1957. On Dec. 7, 1956, she was seen by her physician because of fever and parotid swelling. A diagnosis of mumps was made. There had been an exposure to the disease three weeks previously. Ten days after the onset of the parotitis, a petechial eruption appeared over the lower extremities, and thrombopenia was found to be present. She was admitted to a hospital on Dec. 18, 1956,

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and given 300 mg. of cortisone daily for three weeks. The platelet count approximated 25,000 per cubic millimeter during this time. The cortisone dosage was reduced to 150 mg. daily on Jan. 19, 1957, and this therapy was continued for several weeks.

Because the platelet level failed to rise, she entered the University Hospitals for splenectomy on March 15, 1957. Further questioning at this time revealed that she had taken only salicylates prior to the onset of thrombopenia. There had been no previous history of her having had mumps. On examination she had an appearance resembling that seen in adrenal cortical hyperfunction (Cushing's disease). The temperature and pulse rate were normal, and the blood pressure was 120/70 mm. Hg. There was an acneiform eruption over her face and shoulders, and a few abdominal striae were present. The liver and spleen were not palpable. A few scattered petechiae were present on the legs.

Significant laboratory data showed a hemoglobin level of 12.4 Gm. %, leukocytes, 8,550 per cubic millimeter with 75% neutrophils, and a platelet count of 23,000 per cubic millimeter. The bleeding time was 10½ minutes and the clotting time 3½ minutes. The reticulocyte count was 2.2%. Clot retraction was normal. Normal serum protein values were found. The serum iron level was less than 20 μg. per 100 ml. Findings on three L. E. cell tests were negative. The direct and indirect Coombs' test results were negative. The complement-fixation test for mumps showed positive findings in a titer of 1:32. A four-day fecal urobilinogen excretion was normal. Sternal bone marrow aspiration on March 19, 1957, revealed a normal number of megakaryocytes, but they were morphologically abnormal in appearance.

On March 22, cortisone therapy was discontinued and she was given 40 mg. of prednisone daily. The platelet levels continued to fluctuate between 16,000 and 80,000 per cubic millimeter. Splenectomy was carried out on April 10, 1957. The spleen weighed 150 mg. and grossly and microscopically appeared normal. The platelet count just prior to surgery was 54,000 and 12 days later 826,000 per cubic millimeter. The steroid intake was gradually reduced, and this therapy discontinued on April 30, at which time the platelet count was 630,000 per cubic millimeter. When she was discharged on May 7, 1957, the platelet count was 450,000 per cubic millimeter. On follow-up visits it was observed that the thrombopenia had returned. On June 4, 1957, the platelet count was 80,000 per cubic millimeter and steroid therapy was resumed. By June 11, the count was 164,000. Over the succeeding weeks steroid therapy was gradually reduced and finally discontinued on Sept. 3, 1957. At this time the platelet count was 282,000 per cubic millimeter. When last seen on Feb. 4, 1958, she was in good health and the platelet count was 275,000 per cubic millimeter.

Comment.—The foregoing case report emphasizes the seriousness and chronicity of thrombopenia occurring as a complication of mumps. Steroid therapy did not abolish the thrombopenia, but it was helpful in controlling the bleeding tendency. Again, splenectomy failed to achieve any sustained rise in the platelet count.

CASE 3.—A 44-year-old man was admitted to the University Hospitals on April 1, 1958, because of bleeding gums and a generalized petechial eruption over the skin of his body. Seven days prior to admission he had had a severe headache, which was followed two days later by parotitis. Two of his children, aged 5 and 6 years, had had mumps three weeks before the onset of his illness. On the day before entry to the hospital he had noted right testicular pain and tenderness. On the morning of admission he had bleeding of the gums and observed a generalized petechial rash.

The only medicament he had taken prior to his illness was a salicylate. There was no history of mumps. For a number of years he had had a scaly erythematous rash over his cheeks which appeared each spring and fall. He had episodes of wheezing during the ragweed season.

Physical examination revealed a well-developed and well-nourished white man with a normal temperature and pulse rate and a blood pressure of 108/75 mm. Hg. No parotid swelling was present. The liver and spleen were not felt. The right testis was enlarged and quite tender. A severe petechial eruption was present on the skin of his neck, hard palate, arms, and legs.

The laboratory data revealed occasional erythrocytes in the urine. The hemoglobin level was 14.1 Gm. %, leukocytes, 6,800 per cubic millimeter with 66% neutrophils; platelet count, 12,000 per cubic millimeter, and prothrombin time, normal. A study of aspirated sternal bone marrow revealed slight hypoplasia with a moderate increase in the number of megakaryocytes. The complement-fixation titer for mumps was 1:128.

During the first six days of hospitalization, the platelet counts fluctuated between 8,000 and 34,000 per cubic millimeter and petechiae continued to appear. Beginning on April 7, 1958, 60 mg. of prednisone was given daily. Within 48 hours the painful orchitis had subsided, and by April 16 the platelet count rose to 110,000 per cubic millimeter. The dosage of prednisone was gradually reduced to 35 mg. daily, but further reduction was followed by a diminution in the number of platelets. On April 24, the platelet count was 52,000 per cubic millimeter and the dosage of prednisone was increased to 45 mg. daily. During the following three weeks the maximum platelet count was 95,000 per cubic millimeter. On May 15, 1958, the dosage of prednisone was reduced, so that by June 5, 1958, the platelet count had stabilized at about 100,000 per cubic millimeter. Finally, on July 7, 1958, the prednisone therapy was discontinued, the platelet level being 139,000 per cubic millimeter. He was asymptomatic.

Comment.—This man had two acute complications of mumps, orchitis and thrombopenia. The hemorrhagic tendency was serious, but persistent steroid therapy controlled the bleeding. It is interesting that, although splenectomy was not carried out in this patient, the natural course of the thrombopenic state was similar in character to that in the other two patients.

Summary and Conclusions

Mumps is not an uncommon infection of adult life. The complications can be painful and serious; they include orchitis and meningoencephalitis. Less commonly, pancreatitis and oophoritis occur. Thrombopenia must be added as a complication, and this is potentially serious. The pathogenesis of these complications is not clearly understood. Although direct invasion of the tissues by virus may be responsible for the inflammatory reaction, the possibility also exists that a state of acquired hypersensitivity may be the cause.

There is now substantial evidence showing that the inflammatory complications of orchitis and meningoencephalitis can be controlled by therapy with adrenocorticosteroids.[2] The present report indicates that steroid therapy is also effective in thrombopenia occurring as a complication of mumps. In two of the three patients steroid therapy was insufficient to correct the platelet deficiency but did control the bleeding tendency. In a third patient with orchitis

and thrombopenic purpura, steroid therapy alone controlled both complications. It is suggested that mumps should be considered as a possible causative factor in cases of "idiopathic" thrombopenic purpura. The clinical course of these three patients suggests that splenectomy was not definitive in terminating the thrombopenic state. Steroids did control the bleeding tendency.

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OBJECTIVES FOR STATE MEDICAL SOCIETY TRAFFIC SAFETY COMMITTEES

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The cooperation of the medical profession is needed in the field of traffic safety, and effective leadership can be supplied by committees appointed by state medical societies. Their function should be to guide and stimulate; they can supply needed information to interested groups, seek to improve existing laws that affect automobile traffic, and cooperate in special projects of research and education. In addition to carrying out the strictly medical aspects of its activities, a traffic safety committee can do much to promote programs of training for student and adult drivers, supplement the efforts of civic groups and governmental agencies, and, in general, set good examples of driving habits, law observance, and good citizenship.

It is my belief that every state medical society should have an active traffic safety committee or should assign a traffic safety program to some appropriate existing committee of the state society. The Committee on Medical Aspects of Automobile Injuries and Deaths of the American Medical Association can develop suggested health standards for driving automotive vehicles, but these standards must be tailored to the individual needs of the separate states. Fortunately or not, the legal problems attendant on driving on the highways of the United States are functions of state governments rather than of the federal government. Educational campaigns to improve driving abilities are largely effective on a state basis. For this reason the successful cooperation of the medical profession in the field of traffic safety will be even more dependent on what state medical societies do than on what the A. M. A. does.

What can a state medical society do about this problem? I say "state medical society" rather than just the traffic safety committee of a state medical society, for success will come only as all the members of a state medical society contribute to meeting the problem under the leadership of a traffic safety committee. The job of the committee is to guide and stimulate. By itself, it can do little.

How large should such a committee be, and who should be on it? Five should be a minimum number. A committee of over 10 or 12 members becomes unwieldy. Interested members should come from many fields of medicine, not just one or two. Such areas would include general surgery and its subbranches most interested in trauma, general practice, internal medicine, eye, ear, nose, and throat, psychiatry, public health, and other related fields.

Such a committee may well spend one meeting or more just in finding out what the traffic situation is in that particular state, determining statistics, finding out something about the more important existing traffic laws, and meeting with a representative of the state police and state driver licensing agency. It will soon discover that there are many others just as interested in this traffic safety problem as physicians are and that the job is a cooperative one with no easy answers and no one master solution. The members of the committee will find that there is an avalanche of facts and present programs about which it knows very little. After looking over the field carefully, it should then settle on one or two projects at a time which are necessary and

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reasonably attainable within a few years at most. All progress is agonizingly slow to those who are enthusiasts!

There is a large group of medical and a smaller group of nonmedical projects which such a committee might consider in view of the primary needs in an individual state. The following objectives are offered as suggestive only and not as all-encompassing.

Medical Objectives

The committee should first aim to provide the practicing physician with technical medical information regarding driving limitations for his patients. This can be done by drawing attention to (1) the A. M. A. manual soon to be published: "Medical Guide for Physicians in Determining Fitness to Drive a Motor Vehicle"; (2) special traffic safety editions of the state medical society journal, with the authors of the articles primarily, but not necessarily, from that state (the authors need not all be doctors); a recent such issue of the *Journal of the Michigan State Medical Society* contained articles with the following titles: "Are Your Patients Physically Qualified to Drive?" "Use of Chemical Tests for Intoxication in Michigan Law Enforcement," "Drugs and Driving," "The Highway Accident Problem in Michigan and What Has Been Done About It," "Automotive Crash Injury Research in Michigan," "Traffic Accidents and Safety," "The Speeding Ambulance," and "Emotional Problems in Driving"; (3) both intramural and extramural postgraduate courses for practicing physicians in both prevention and treatment of traffic injuries; and (4) appropriate information through the secretary's letter as well as other special media from the office of the state medical society.

The second objective should be to inform the driving public, through the use of proper media, of those medical conditions which may adversely affect driving proficiency. This can probably be done best by an effective distribution of the A. M. A. booklet, "Are You Fit to Drive?" either by the state medical society alone or in cooperation with other interested groups, such as industrial and insurance companies. Placement in local offices for driver licensing would be most effective if enough copies are available. Information to the public can also be given through the usual media of the press, television, radio, luncheon clubs, parent-teacher associations, and other groups. And let us not forget one of the most important means of all, i.e., individual contact with our patients!

Third, the committee should become familiar with the individual state's driver licensing laws and seek to improve them. This is a long, slow process and will not be accomplished overnight. It may take repeated years of introduction of legislation before it even gets out of a legislative committee and more years yet before it becomes law in an unemasculated form.

Fourth, the committee should cooperate with special projects, such as the Cornell Crash Project and other programs of medical research in the traffic safety field. This will mean work, but it will yield results that can be gained in no other way. The facts of traffic epidemiology and research should guide our efforts.

Fifth, the committee should seek to encourage the teaching of first-aid courses. Such courses, if they are to receive Red Cross recognition, must be taught either by trained lay instructors or by physicians.

Sixth, the committee should promote state and municipal standards for ambulance operators and equipment. Flint, Mich., has such regulations, and the Michigan State Medical Society is considering legislation of this type for possible introduction in the next session of the legislature.

Seventh, the committee should cooperate with state departments of public instruction in the securing of adequate health standards for school bus drivers.

Eighth, the committee should seek to promote, particularly in the larger county societies, traffic safety committees for county medical societies.

Nonmedical Objectives

There are several nonmedical fields of traffic safety in which it is advantageous and proper for a state medical society to lend its cooperation, even though in most instances the more strictly medical fields should receive a first priority of time and effort.

First, inclusive student driver training legislation should be a goal for each state. Comparison studies have pointed up the fact that students who have passed behind-the-wheel student driver training courses in high school have approximately one-half the accident rate of those who have not. In most states at least one-fourth of all traffic fatalities involve drivers 25 years of age and under, and in some states this figure is closer to one-third. In all the public schools of the United States, just over one-third of the students reaching legal driving age are able now to take behind-the-wheel driver training. Total figures for the private and parochial schools are not available, but they are undoubtedly much less than the one-third mention for public schools.

Benefits from a comprehensive student driver training program would be cumulative from year to year in this younger age group, probably averaging a total reduction of approximately 8% in the over-all traffic death rate when the program has been in existence for 10 years and allowing for a one-third coverage at the present time. Based on the total annual traffic toll of 38,000, this would mean a reduction of 300 deaths the first year, with increased savings of an additional increment of 300 lives each year until approximately 16,500 lives

would be saved over a 10-year period. At least a part of the marked drop in traffic fatalities in Michigan over the past two and one-half years (over 25%) has been attributed to an inclusive driver training program.

Traffic experts say that the attitudes of individual drivers play a large part in the accident picture. Nowhere is there a better chance to develop, en masse, good attitudes along with the technical skills than in a comprehensive program of student driver training, for such courses must be taught by trained teachers with minimum standards for the subject material and the amount of time behind the wheel.

What is envisioned in such a comprehensive program? Michigan legislation requires that each teenager must wait until he is 18 to get his driver's license unless he has first passed an approved student driver training program, in which case he may get his license at the age of 16. This is the carrot in front of the donkey that gets the students into the courses! Every public high school must offer the course if it is requested by students.

In return for the fact that driver education is more expensive per pupil than other courses offered in high school, the state subsidizes the schools approximately $20-$25 per pupil, this money being secured by earmarking 50 cents a year from the driver license fee. Without some such subsidy, the schools, for the most part, would not be able to finance comprehensive training coverage, and it seems fair for those driving on the highways to help insure the young drivers becoming safer drivers. The young driver himself will have repaid the cost of his subsidy after paying for his driver license fees over a 45-year period.

In Michigan, private and parochial students who want to take the course may do so at a nearby public high school, with the public high school receiving the subsidy.

In the current critical examination of school curriculums, the place of driver education has been attacked by some, including Mr. Adlai Stevenson. I am sure that Mr. Stevenson and the other critics have not examined the available statistics on the problem. Furthermore, it is not necessary that basic subjects be sacrificed for driver education. The small high school in my community requires 20 units instead of the customary 16 for graduation, and 16 of these 20 must be in basic subjects. In Jackson, Mich., the extra time for driving is taken from physical education and not from basic subject time. Many of the larger high schools conduct courses in the summer for those unable to take them during the school year. Our future scientists will not suffer for being taught driver education while in high school, and, because of this training, they will stand a greater chance of staying alive long enough to be scientists! There is no hint that school critics would toss physical education out of the curriculum, and yet in terms of conservation of human life we must conclude that there is an even greater potential in a comprehensive student driver training program than in a physical education program.

Second, we should also urge the formation of special schools for adult driver training and for chronic traffic offenders. This is already being done in some states, including the state of Michigan, with schools organized on a fee basis which meets all their costs and adults either going voluntarily or being sent there by the courts for remedial instruction.

Third, we should cooperate actively in state and local citizens' traffic safety committees. Such committees are eager for support, on many issues they need our advice, and on safety matters of public education and proposed legislation we may need theirs! A citizens' traffic safety committee is much like a military division which is composed of different types of troops, not all of whom may be in action at the same time but who still need each other's support. We also must not forget that, as doctors, we also are citizens and have responsibilities apart from our profession.

Fourth, we should early offer the facilities of the state medical society to the governor, the state police, the state's licensing authority, and any other governmental agency on the state or local level which is attempting to meet the traffic safety problem. I scarcely need to point out that a by-product of these activities can be excellent public relations to the profession in the state.

Fifth, we should discipline ourselves and encourage our colleagues to set good examples in driving habits and law observance. There are times when, perhaps, it seems necessary for us to go faster than the speed limits and to take chances, yet, like a speeding and red-light crashing ambulance which kills more lives than it saves, the speeding doctor may be more of a health hazard than a health protector at times! Let us take the two-by-four out of our own eye before we start looking for the splinter in the other driver's eye!

Conclusions

A traffic safety committee of a state medical society must be more than just a window-dressing committee. It should carefully examine possible courses of action and programs for the society to undertake. The committee members and the society members they represent should come to see that, like anything else of value, a worthwhile traffic safety program will cost something in terms of time, effort, money, and sometimes, perhaps, even changed attitudes.

Finally, we can take the advice which Stonewall Jackson once gave to his younger officers: "Never underestimate yourself in action; never overestimate yourself in the official report."

117 S. Bridge St.

USE OF PROMETHAZINE (PHENERGAN) HYDROCHLORIDE IN OBSTETRICS

REPORT OF A TWO AND ONE-HALF YEAR SURVEY

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Sedation and analgesia during the first stage of labor have been induced in more than 7,500 obstetric patients during a two and one-half year period by a regimen involving use of promethazine (25 to 100 mg. by deep intramuscular injection) and meperidine. The hospital charts of these patients have been compared with those of obstetric patients, during the two and one-half years before promethazine was used, with respect to maternal, fetal, and neonatal mortality, prematurity, duration of labor, and frequency of need for resuscitating the infant. The data showed that promethazine was a safe and effective tranquilizer, rendered labor less unpleasant, and reduced the need for those analgesics and anesthetics which have undesirable side-reactions. A shortening of labor was found and was particularly significant in uncomplicated primiparous cases. Resuscitation of the infant was almost never necessary. The average total dose of promethazine was 56.5 mg., and its effect in reducing the total amount of meperidine needed was convincingly demonstrated.

Our efforts to improve present methods for relief of pain of normal labor, as well as for management of dystocia, and at the same time to reduce perinatal mortality have led us to investigate a number of compounds credited with a relaxant action on the cervix. It is a common observation that labor is more difficult and dilatation unusually slow in the frightened, tense, and highly emotional patient.

Psychological preparation for parturition, although an important factor in prenatal care, has limited usefulness as the sole means of managing labor and delivery. Hypnosis is suitable for few patients, and the "childbirth without fear" concept popularized by Grantly Dick-Read is satisfactory for only about 25 to 30%, according to this author himself. In the great majority of cases, therefore, analgesic and sedative drugs are the only recourse. No drug, however, satisfies all criteria: (1) no increase in risk to parturient and fetus, (2) no interference with the labor mechanism, (3) no clouding of the mental faculties of the patient, (4) convenience of administration, and (5) promptness of action. All conventional agents, such as barbiturates and narcotics, are readily transmitted through the placental circulation, with well-known deleterious effects, and, in dosages within the limits of safety for the fetus, they are usually far from adequate for the needs of the mother.

Since fear-induced discharge of epinephrine increases the cervical tonus, we tried, in our parturient patients, to block the release of epinephrine with agents that depress the sympathetic nervous system (dihydroergotamine, dihydroergocornine, and similar substances). The use of these agents has now been largely abandoned in this hospital, and greater attention has been directed toward the potentialities of the various phenothiazine compounds with suppressive activity on the reticular formation of the central nervous system. Animal experiments [1] have shown that chlorpromazine hydrochloride (in doses of 3 to 6 mg. per kilogram of body weight) prevents the altering response to pain and that promethazine hydrochloride (in doses of 5 to 10 mg. per kilogram) produces the same effect.

Our first report [2] described the results of clinical studies employing combinations first of chlorpromazine with meperidine hydrochloride and then of promethazine with meperidine for sedation and analgesia during the first stage. The action of chlorpromazine proved most unpredictable, and labor appeared prolonged. The patients in whom adequate sedation was achieved showed evidence of decreased muscle tone; such limpness was believed partly to account for the increased duration of labor. Combination of promethazine with meperidine, on the other hand, was highly effective and produced results as predictable and analgesia as satisfactory as with twice the dose of meperidine alone. In consequence of these initial trials, more than 75% of the obstetricians and general practitioners on the staff of this hospital now use promethazine and meperidine in varying combinations for routine sedation during labor. Since predelivery medication is administered entirely at the discretion of the attending obstetrician, there is considerable variation in the volume and timing of the doses. In some cases both meperidine and promethazine are administered together; in others, the doses are administered in succession, from one-half hour to two hours apart. Single doses of each agent range from 25 to 100 mg. Promethazine is always administered by deep intramuscular injection.

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Since the publication of our first report,[3] more than 7,500 obstetric patients have been given sedation under this regimen. We have reviewed their charts and compared them with those of the patients in whom delivery was performed in the two and one-half years prior to the use of promethazine. All cases of infant morbidity and fetal and neonatal deaths have been reviewed in detail (tables 1, 2, and 3); also, the records of 263 consecutive unselected patients given this sedation in 1957, who were delivered of 265 infants (including two pairs of twins), were studied in detail. The results of these reviews will be presented here. We believe they will provide an adequate picture of the over-all results.

TABLE 1.—*Yearly Analysis Reports of Obstetric Data at Grace Hospital*

	Prior to Use of Promethazine			After Use of Promethazine	
	1953	1954	1955	1956	1957
Total births, no.	7,629	7,609	7,844	7,987	8,058
Neonatal deaths, full term and premature, no.	68	93	57	76	57
Rate per 1,000 live births, %	8.99	12.7	9.6	8.8	8.87
Neonatal deaths, term, no.	9	16	7	11	13
Rate per 1,000 live births, %	3.48	3.82	2.50	3.75	4.53
Neonatal deaths, premature, no.	14	23	20	15	14
Rate per 1,000 live births, %	5.42	8.79	7.15	5.14	4.57
Stillbirths, fetal mortality, no.	24	22	20	29	29
Rate per 1,000 live births, %	9.13	8.5	7.03	9.7	9.5
Stillbirths, premature, no.	14	9	7	15	23
Rate per 1,000 live births, %	5.42	3.44	2.50	5.14	7.52
Premature infants, discharged alive and well, no.	62	83	80	80	67
Maternal deaths, no.	0	0	1	1	0

Description of Series and Drug Administration

More than 7,500 patients were treated with promethazine. The neonatal and fetal mortality rates were not appreciably altered (table 1), and, in all, maternal sedation and anesthesia can be ruled out as a cause of death. The pulmonary neonatal morbidity, however, has shown a definite improvement. The decrease in neonatal pulmonary morbidity we attribute to reduction in the amount of respiratory-depressant agents (such as narcotics and barbiturates) required to control the discomforts of first-stage and second-stage labor and decrease in the level of general anesthesia necessary for delivery. During the past two and one-half years (July, 1955, through December, 1957), since the obstetric use of promethazine was initiated, the need of infant resuscitation has become so rare that the members of the resident staff have complained they are getting no training or experience in this important phase of infant care.

Paradoxically, with the decrease in the amount of narcotics used labor rooms have become quiet and peaceful. Except in the cases managed by the few physicians who do not prescribe promethazine, it is most unusual to hear patients in labor crying or complaining bitterly of their pains. The elimination of apprehension not only has reduced the discomfort of the patients but has enabled the case room staff more easily to evaluate their progress and has lessened the tenseness, fatigue, and irritability of the nurses in charge.

A detailed study of 263 consecutive patients treated with promethazine was made. Of these patients, 46% were primiparas. Ages ranged from 14 to 44 years.

Pregnancy had proceeded without incident in 214 (81%). Complications in the remainder included two cases of preeclamptic toxemia. Moderate to excessive vomiting during pregnancy had occurred in 17 patients.

Gestation was of normal duration in 89%. In 3% labor was premature, and 8% of the patients went into labor at 41 to 43 weeks.

On admission, about 75% appeared calm or were able to conceal their natural nervousness and fear of pain, while the other 25% were openly frightened and apprehensive.

Dosage.—Medication was usually administered according to the plan followed in the initial study; i. e., when the patient began to complain unduly of her discomfort, 25 to 50 mg. of promethazine and 50 mg. of meperidine was administered intramuscularly regardless of the extent of dilation. Thus, many patients, especially older primiparas and those whose labor was associated with complications (23 patients), received the initial dose early in the first stage. The dose was repeated at

TABLE 2.—*Analysis of Full-Term Neonatal Deaths by Year*

Condition	1953	1954	1955	1956	1957
Respiratory					
Hyaline membrane disease	1	5	2	1	2
Fetal anoxia	2*	...	1†	1‡	...
Congenital atelectasis (one of twins)	...	1	...	...	...
Acute interstitial pneumonitis	...	...	1	...	...
Neonatal asphyxia (cause undetermined)	...	...	...	...	1
Cardiac					
Transposition of great vessels	...	1	...	1	1§
Tricuspid valve incompetency	...	...	...	1	...
Tetralogy of Fallot	...	...	...	1	...
Congenital cor bilocular	...	...	...	...	1
Congenital cor triloculare	...	...	...	...	1
Rh incompatibility					
Erythroblastosis	1	1	...	2‖	...
Pulmonary infarction (during replacement transfusion)	...	...	...	...	1
Hemolytic disease (twins)	...	...	...	...	2
Other					
Spina bifida	2	...	...	...	...
Congenital diaphragmatic hernia	1	1	...	...	...
Congenital dysplasia of cerebrum	1	...	...	...	...
Congenital hypoplasia of kidneys	1	...	...	...	...
Congenital agenesis of kidneys	...	1	1	...	...
Massive hemorrhage of adrenals	...	...	1	...	...
Subarachnoid hemorrhage	...	...	1	1¶	2¶
Intracranial hemorrhage (from difficult labor)	...	...	...	1	...
Anencephaly	...	...	...	1	...
Mongolism (primary atelectasis)	...	...	...	...	1
Vacuolation in central nervous system (possible x-radiation effect)	...	...	...	...	1
Totals	9	10	7	11	13

*Placenta previa.
†Premature separation of placenta.
‡Cause undetermined.
§Pulmonary embolism during replacement transfusion.
‖Difficult delivery.
¶Aorta and pulmonary vessels.
**One difficult rotation and delivery and one breech presentation.

the discretion of the labor room nurses or according to the individual physician's orders and, occasionally, if indicated, in an amount larger than that used initially. Although we discouraged the use of other agents, a few obstetricians, in rare instances, supplemented the medication with a small dose of some other narcotic or barbiturate.

For the individual patient the total dosage of promethazine ranged from 25 mg. (14%) to 125 to 150 mg. (5%). Fourteen per cent required 75 mg. and 11% 100 mg. The majority (56%) obtained adequate sedation with 50 mg. In uncomplicated cases meperidine was required for analgesia in total doses of 25 to 200 mg. Eighty per cent received 50 or 100 mg. In protracted cases with abnormalities of presentation or other difficulties and in trial labor, pain was adequately relieved in 50% with 50 or 100 mg. of meperidine. The remainder received 125 mg. or more, and 275 mg. was required by two patients (table 4).

Table 3.—*Analysis of Term Stillbirths by Year*

Condition	1953	1954	1955	1956	1957
Antepartum deaths					
Toxemia of pregnancy	1	...	...	...	...
Rh incompatibility	2	2	2	1	2
Placental infarction	1	1	3	...	...
Fetal anoxia	2*	...	2§	...	2§
Antepartum hemorrhage	...	3‡	1	4	...
True knot in cord	...	1	...	...	...
Nuchal cord	...	...	...	...	1
Hydrocephalus	...	...	...	...	1
Unknown cause	...	...	2	1	...
Totals	6	7	10	6	6
Intrapartum deaths					
Breech presentation	2†	...	1‡	...	...
Premature separation of placenta	1	1	...	4	...
Siamese twins	1	...	...	...	...
Fetal asphyxia (traumatic delivery)	...	1	...	...	...
Intra-alveolar hemorrhage	...	1	...	...	...
Placental insufficiency (one of twins)	...	...	1	...	...
Prolapse of cord	...	...	...	1	2
Premature rupture of membranes	...	...	...	1	1‖
Hydrocephalus (craniotomy)	...	...	...	2	...
Pulmonary edema (cause undetermined)	...	...	...	...	1
Congenital atelectasis (cause undetermined)	...	...	...	...	1
Totals	4	3	2	8	5

* Cause undetermined.
† Difficult delivery.
‡ Placenta previa.
§ Cord around neck.
‖ Prolonged labor.
¶ With asphyxia; cause not definitely determined.
# Intrauterine pneumonia.

Although most patients (61%) received the last dose of meperidine one to two hours before delivery, the timing of this dose ranged from eight minutes to 18 hours before delivery.

For the entire 263 patients, the average total dose of promethazine was 56.5 mg. and of meperidine 93.7 mg. (table 5).

Results

Average Duration of Labor. In uncomplicated cases, the average length of the first stage, for primiparas, was about 11 hours and of the second stage about 35 minutes. The total length of uncomplicated first-stage and second-stage labor for primiparas averaged 11 hours and 35 minutes. For the multiparas in this group, the first stage averaged seven hours, 30 minutes, and the second stage 20 minutes. The total length of uncomplicated first-stage and second-stage labor in the multiparas averaged seven hours and 50 minutes (table 6).

Table 4.—*Distribution of Total Dose of Meperidine Required for Adequate Analgesia Throughout Labor*

Meperidine, Mg.	Uncomplicated Labors, %	Protracted Labors, %
25	3	...
50	40	15
75	1	...
100	40	35
125	1	]
150	7	]30
200	8	]
250-275	...	20*

* Four patients.

For difficult and protracted cases, in which rotation and delivery with midpelvic forceps was required, the total duration ranged from 15 hours and 10 minutes to 35 hours and 15 minutes, with an average of approximately 27 hours and 50 minutes.

Trial labor, conducted in five primiparas, ranged from 8 to 34 hours and averaged 26 hours and 23 minutes (table 6).

Presentation.—Eighty-eight per cent of the fetuses were in cephalic presentation. Difficulties in descent and abnormalities of position and presentation, such as transverse lie, transverse arrest, and shoulder dystocia (two cases), occurred in 6%. The breech presentation occurred in 3%. In the remaining 3%, cephalopelvic disproportion, small outlet, deep transverse arrest, and presence of Bandl's constriction ring (in a 31-year-old primipara) necessitated cesarean section.

Anesthesia.—Delivery was performed in 71% of patients with uncomplicated cases under general anesthesia. Intermittent inhalation of nitrous oxide and oxygen was used for analgesia during painful second-stage contractions; for delivery, deeper anesthesia was induced with cyclopropane or trichloroethylene. The average duration of general anesthesia was about 38 minutes. Peridural anesthesia was used in 28% of patients. Two multiparas were delivered without use of anesthetic agents.

Table 5.—*Potentiation of Analgesic Action of Meperidine by Promethazine*

	Patients, No.	Promethazine, Av. Total Dose per Patient, Mg.	Meperidine, Av. Total Dose per Patient, Mg.
Routine sedation in controls (prior to use of promethazine)	435	...	156.8
1955 series	300	58.5	98.0
1957 series	263	56.5	93.7

Rotation and delivery with midpelvic forceps was performed with the patient under anesthesia with nitrous oxide and trichloroethylene (six patients) or under peridural anesthesia (nine patients). Average duration of anesthesia in this group was about one hour and five minutes.

Cesarean sections were performed with the patient under subarachnoid block anesthesia with use of tetracaine hydrochloride.

Delivery.—Delivery was spontaneous in 50% of the patients (28 primiparas, 104 multiparas), and for 42% low forceps were used (77 primiparas, 33 multiparas), in a few cases after manual rotation. For 5% (10 primiparas, 5 multiparas) midpelvic forceps rotation and delivery were required.

In 55% of patients with vaginal deliveries episiotomy was performed (87 primiparas, 57 multiparas), and 6% of patients experienced lacerations. The umbilical cord was wound around the neck of the fetus in five cases. The placenta was retained in two primiparas; manual extraction was performed in one of these after one-half hour. Of the eight cesarean operations (3%), one was a repeat section.

Mortality.—There were three antenatal deaths (a fetal mortality of 1%). One was in a stillborn female, delivered spontaneously with shoulder presentation, of a 35-year-old multipara at 42 weeks' gestation. Labor was medically and surgically induced 48 hours after rupture of the membranes. Death was attributed to intrauterine pneumonia, intramedullary adrenal hemorrhage, and septicemia. The second was in a stillborn male of a 26-year-old multipara by spontaneous vertex delivery after 26 hours' labor at 40 weeks' gestation. Death was believed to be the result of placental separation, since no fetal heart sounds had been detectable for two days prior to induction of labor. The third fetus in this group was aborted at 28 weeks' gestation; the mother was a 26-year-old primipara. There were no maternal deaths.

Infants.—Ninety-five per cent of the 262 viable infants breathed and cried spontaneously within one minute of delivery; 3.5% required mild resuscitation with removal of mucus from the pharynx and administration of oxygen by mask, and 1.5% (four infants) showed some respiratory depression and received, in addition to oxygen in positive-pressure breathing, intravenous injection of a narcotic antagonist (nalorphine hydrochloride, 0.2 mg.).

One child in the latter group was delivered with low forceps, with the mother under peridural anesthesia for 60 minutes, after 21 hours and 50 minutes' labor. The mother had received a total of 150 mg. of meperidine and 100 mg. of promethazine during labor. In the second case, the umbilical cord was wound around the neck; transverse arrest and shoulder dystocia necessitated forceps rotation and delivery with the mother under peridural anesthesia for one hour and 54 minutes, after labor of 15 hours. The predelivery medication of the mother had consisted of 250 mg. of meperidine and 150 mg. of promethazine. In the third case, the infant was delivered by cesarean section of a mother who had shown symptoms of preeclamptic toxemia. This patient had received 3 grains (0.19 Gm.) of phenobarbital (Luminal) sodium and ¼ grain (15 mg.) of morphine, in addition to 50 mg. of promethazine in the preanesthetic medication. The fourth infant, delivered spontaneously after 12 hours and 50 minutes' labor, showed evidence of asphyxia as a result of a tight nuchal cord. The mother had received 200 mg. of meperidine and 75 mg. of promethazine for predelivery analgesia and sedation.

Nine of the 262 viable infants had either congenital malformations (six infants) or symptoms suggesting brain damage (three infants, or 1% of the series).

The infants exhibiting signs of neurological damage included one male in whom cerebral palsy was probable (he had been delivered of a primipara, with low forceps, under peridural anesthesia of two hours' duration after 20 hours of labor), one male with symptoms of meningism (delivered of a multipara, with low forceps, under general anesthesia for 30 minutes after about 15 hours' labor), one female with symptoms of cerebral irritation (delivered of a primipara, with low forceps, under peridural anesthesia for 45 minutes after 20 hours of labor, and with a tight nuchal cord).

Postpartum Period.—Vomiting occurred in four patients after delivery and was controlled in each case by an additional injection of 25 mg. of pro-

TABLE 6.—*Average Duration of Labor*

	Primiparas					Multiparas				
	Patients, No.	Stage 1		Stage 2		Patients, No.	Stage 1		Stage 2	
		Hr.	Min.	Hr.	Min.		Hr.	Min.	Hr.	Min.
Eastman, N. J.: Williams Obstetrics, ed. 10, New York, Appleton-Century-Crofts, Inc., 1950		16		1	45		11		1	
DeLee, J. B., and Greenhill, J. P.: Principles and Practice of Obstetrics, ed. 9, Philadelphia, W. B. Saunders Company, 1947		16		1	45		12			15-30
Present study										
Controls	130	12	55	1	12	150	7	26		16
Chlorpromazine and meperidine	127	16		1		72	10			14
Promethazine and meperidine (1955)	135	11	47	1	7	165	8	55		19
Promethazine and meperidine (1957)	139					143				
Uncomplicated deliveries	105	11			35	135	7	30		20
Abnormally difficult deliveries*	10	26	8		50	5†	24		1	
Trial labor before cesarean section‡	5									

* Abnormalities in these 15 cases not attributable to predelivery medication.
† Cesarean operations for all multiparas and for one primipara were performed without trial labor.
‡ Includes one multipara delivered with midpelvic forceps after total labor of 55 hours, 15 minutes.

methazine. Two patients experienced postpartum hemorrhage, one on the 1st and one on the 10th day. Dehiscence of the episiotomy occurred in one patient. One had endometritis, a second pyelonephritis, and a third cystitis. Three complained of pain in the back and coccyx and one of headache (a multipara delivered under general anesthesia). Enlargement of the spleen was observed in one patient; monilial infection of the episiotomy developed in another; and a third had hemorrhoids.

Complications developed in six infants during the postpartum period; infection of the umbilical stump, thrush of the mouth, and impetigo on the face occurred in each of three infants. Purulent conjunctivitis occurred in two infants. A toxic erythema developed in one who had received a narcotic antagonist. No bacteria were found in cultures of nose and throat.

Ninety-nine per cent of the infants were discharged in good general condition. Of the remainder, the condition of two was considered "fair" (one infant had a congenital heart lesion and one showed symptoms of meningism). One infant with esophagotracheal fistula was transferred to another service for further evaluation.

Comment

The findings in this survey confirm the impressions obtained in our controlled initial study. We believe the best effect may be achieved by administering 50 to 75 mg. of promethazine intramuscularly early in labor before analgesia is needed. The sedation provided by one dose lasts four to five hours; the dose may be repeated as indicated. As distress becomes more severe, meperidine may be injected intramuscularly in doses of 50 mg.

Before the potentialities of promethazine in the obstetric field were realized, meperidine was used, we feel, in doses larger than were necessary to control the actual pain. Such doses were administered mainly because the parturient was excited and frightened and her appreciation of the contractions was exaggerated. On administration of promethazine early in the first stage, however, the patient is relaxed and relieved of her fears, so that effective labor is soon established, especially in the primipara. She sleeps or rests between pains throughout the course but remains mentally clear; thus, her own estimate of the need of analgesia becomes more reliable.

The atmosphere of the labor room is noticeably quieter; it is rare to hear a patient cry out even at the peak of the contractions. One of us (R. S. M.) thought, on first acquaintance with the labor room here after arrival from Britain, that the patients were "abnormally" quiet. He was surprised to find that the average total dose of meperidine required per patient was quite small. An obstetrician recently returned from New York was similarly impressed and believed the patients were under the influence of heavy doses of sedatives.

The patient arrives in the delivery room in a comparatively unfatigued state and, hence, is better able to cooperate with the anesthetist and obstetrician; she does not resist the anesthetic and under light nitrous oxide anesthesia is able to push effectively with her contractions.

Our experience, in common with that of other workers,[6] suggests that promethazine potentiates all anesthetic agents. Therefore, rapid induction of deeper anesthesia for delivery of the head is accomplished with smaller dosage. Patients are usually awake or can be aroused soon after delivery and repair, although they generally remain drowsy for several hours post partum.

The degree of relief provided by promethazine-meperidine medication is difficult to assess from the patients' statements after delivery. It may be impossible to obtain from multiparas reliable information for a valid comparison with previous obstetric experiences without asking leading questions. However, a multipara will usually state that the contractions were less distressing and that she was better able to relax and sleep in the intervals between pains than in previous labors managed with conventional medication.

The suppressive action of promethazine on the alerting response to pain, as demonstrated in animals, may explain the obvious relaxation produced in the parturient. This is apparently reflected in the shortening of labor [4] (particularly significant in primiparas) and in the definite reduction of the total amount of narcotics required. In our continued experience of two and one-half years with this regimen, we have gradually increased the average total dose of promethazine per patient and have steadily reduced the total amount of meperidine (table 3).

The antihistaminic, antiemetic,[5] antiedema,[6] and atropine-like [7] properties of the compound, as observed by others, have been clinically demonstrated in these patients. No evidences of sensitivity to the medication have developed. Our obstetricians have the impression that the antihistaminic action of the compound is reflected in lessened edema of the tissues traumatized by episiotomy or laceration and in more rapid healing after the repair. The drying action is such that atropine is no longer administered even before anesthetization with cyclopropane, and the strong antiemetic effects have rendered vomiting an extremely unusual experience even during and after use of anesthetic agents that predispose to emesis. A sedative is especially valuable when it reduces the incidence of vomiting and, consequently, the catastrophe of aspiration.

Unlike chlorpromazine and some other ataraxics, promethazine does not alter the maternal blood pressure or pulse rate or unfavorably influence the fetal heart rate. Thus, patients in shock, from whatever cause, are relieved of the additional insult of drug-induced hypotension. Similarly, fetuses in

distress are not embarrassed further by a maternal blood pressure too low to provide adequate transport of oxygen across the placenta.

Promethazine is unaffected by narcotic antagonists. Should the mother have been given narcotics to the extent that either her or her baby's respiratory center is depressed, the antagonists are as effective as if the narcotics had been given alone. The drug is not in itself an analgesic; therefore, when pain is present, the administration of a narcotic or other analgesic is indicated. It has been our experience in these 7,500 obstetric cases and in over 15,000 surgical cases of all types and in all age groups that there are practically no contraindications to the use of promethazine. In a few elderly arteriosclerotic patients, intramuscular injection of over 75 mg. has given rise to a state of confusion and restlessness. This condition has been controlled easily by small doses of meperidine.

Promethazine is not a panacea for all the problems of obstetrics. It is an effective tranquilizer and, as such, renders labor less unpleasant and reduces the need for those analgesics and anesthetics which have undesirable side-actions. It is a safe drug with no undesirable side-effects, and its administration does not interfere with or preclude the use of any other drugs which the physician might wish to use.

Condition of Fetus.—Recent chemical studies [4] of fetal cord and maternal venous blood samples seem to indicate that promethazine either does not enter the placental circulation or does so slowly and in insignificant amounts. However, whether the compound crosses the placental barrier or not appears clinically unimportant, because it obviously has little or no adverse effect on the fetus.

The fetal respiratory centers are evidently benefited by the significant reduction in the dosage of depressant agents required for analgesia and anesthesia in the mother.[3] Spontaneous respiration in the newborn infant is the rule. Resuscitation is almost never required, except when some abnormality of delivery is involved or the infant has been asphyxiated by the winding of the cord about the neck or body. The use of narcotic antagonists has been almost eliminated. On delivery to the nursery, the infants are usually pink, crying lustily, and showing good muscle tone—a circumstance which impresses both pediatricians and nursing staff.

Fetal and Neonatal Mortality.—Analysis of the records covering the period from 1953 through 1957 (i. e., two and one-half years before and two and one-half years after the introduction of promethazine into predelivery medication) shows, first, no significant alteration in the incidence of full-term antepartum and intrapartum deaths. Aside from those caused by congenital anomalies and Rh incompatibility, the majority were (or are assumed to have been) the result of faults in the placenta or cord (table 1). Analysis shows, second, no pronounced difference in the incidence of full-term neonatal deaths (tables 1 and 2). Again, most of these deaths are the result of Rh incompatibility and congenital anomalies. Although the number of deaths from respiratory causes does not show a marked change during the period under review, the over-all incidence of respiratory complications has declined.

Morbidity.—Morbidity in the newborn infant from pulmonary complications, especially atelectasis and pneumonia, showed a significant decrease in the first two and one-half years that promethazine was used.

Since resuscitation of the newborn infant is now so infrequent, drug-induced respiratory depression apparently has been reduced to a satisfactory low level. We feel that, if this is so, neonatal respiratory depression from predelivery medication of the mother is now less important as a cause of neonatal death and morbidity than difficult delivery. However, the fact remains that in premature and complicated labors even small doses of respiratory depressants may be sufficient to upset the delicate balance governing survival.

Summary

The charts for more than 7,500 obstetric patients to whom promethazine and meperidine were administered for predelivery sedation-analgesia were reviewed. These were compared with the records covering the two and one-half years prior to the use of promethazine in obstetrics. Records for 263 consecutive, unselected patients delivered in 1957 were reviewed in detail. Forty-six per cent were primiparas. Labor was premature in 3%.

The average total dose of promethazine per patient has been gradually increased and the total amount of meperidine used consistently reduced. The total dose of promethazine averaged 56.5 mg. and of meperidine 93.7 mg. per patient, including those in whom labor was attended by abnormalities. The results with the promethazine-meperidine combination were as predictable as those from almost twice the amount of meperidine used alone; maternal analgesia and relaxation were vastly superior, and infant morbidity was decreased.

In 92%, labor and delivery were without complication or special difficulties. In 5%, labor was protracted and difficult, necessitating midpelvic forceps rotation and delivery. Cesarean section was performed in 3%. In none of these complicated cases was medication a contributing factor. The fetal mortality was 1%, and there were no neonatal deaths.

The analgesia of anesthetics and analgesics is potentiated by promethazine without any alteration of their action on the respiratory center; therefore, smaller doses are effective but less depressing. Atropine is no longer used before induction. Vomiting is rare, even with use of anesthetics that predispose to emesis.

The medication does not alter the vital signs in the mother or affect the fetal heart rate. This is of benefit to patients in shock and to infants who already have hypoxia.

Ninety-five per cent of the viable infants cried spontaneously within one minute of delivery. Resuscitation is almost never necessary, and the use of narcotic antagonists has been almost eliminated.

There has been little or no change in the incidence of full-term antepartum, intrapartum, and neonatal deaths. Morbidity in the newborn infant from pulmonary complications has been reduced. The shortening of labor is particularly significant in uncomplicated primiparous cases.

The combination of meperidine and promethazine for patients in labor is recommended, since this regimen provides superior sedation-analgesia and is attended by greater safety than is use of meperidine alone.

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The promethazine hydrochloride used in this study was supplied as Phenergan hydrochloride by Poulenc, Ltd., Montreal, Canada.

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CAUSES VERSUS SYMPTOMS IN AUTOMOBILE ACCIDENTS

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Recently, a member of the American Medical Association forwarded to the Department of California Highway Patrol a request that a representative of this department present a paper before the Committee on Medical Aspects of Automobile Injuries and Deaths. The context of the paper was to be "Causes of Automobile Accidents." This request seemed appropriate, as the California Highway Patrol presently employs approximately 2,000 officers who are well trained in accident investigation and, during the past 30 years, has carefully analyzed investigation reports covering more than 2 million automobile accidents.

Data secured from these reports are coded, tabulated, and exposed to the mathematical scrutiny of an electronic computer capable of calculating

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Read in the Symposium and Panel Discussion on Motor Vehicle Accidents and Their Prevention in the Session on Traffic Accidents before the Section on Miscellaneous Topics at the 107th Annual Meeting of the American Medical Association, San Francisco, June 25, 1958.

Basic causes of automobile accidents cannot be classified in such terms as speeding, wrong side of the road, or drunken driving. True causes must be listed in such terms as anxiety, causing preoccupation; heart attack, resulting in loss of consciousness; or prolonged use of alcohol, resulting in psychotic condition. The most effective method of treating the problem of automobile deaths and injuries is the attacking of the basic causes, thereby effecting a reduction in the number of accidents. The most effective approach to accident prevention is through active, planned use of methods available only to the medical profession.

mathematical correlations at the rate of 200,000 per minute. The finished analytic summaries are transmitted to the research and development officer for his review prior to dissemination.

Certainly, the research and development officer should have a wealth of information regarding the causes of traffic accidents. However, when the request from the A. M. A. was referred to me, I was forced to reply that the factual data regarding accident causes were almost nonexistent. This statement appeared so unreasonable that I was asked to appear before the Committee and explain it. The basis for the statement was as follows.

The Search for Basic Causes

For 30 years those agencies responsible for dealing with the social illness called traffic accidents have adopted almost the same method as the medical field dealing with the common cold. In other words, they have constantly explored methods of treatment of the symptoms of the illness and have realized almost no progress in attempts to analyze basic causes.

This fact will become self-evident if one considers such subjects as types and degrees of injuries, chemical tests to determine intoxication, and effect of seat belts. Each discussion may provide assistance to accident prevention agencies but will not further the search for facts regarding basic causes. The reason for this is that basic causes cannot be classified in such terms as speeding, wrong side of the road, or drunken driving. True causes must be listed in such terms as anxiety, causing preoccupation; heart attack, resulting in loss of consciousness; or prolonged use of alcohol, resulting in psychotic condition.

The validity of this conclusion is borne out by a recent analysis of coroners' reports covering motor vehicle deaths submitted to this department. In 653 reports submitted by an agency that had access to adequate postmortem examination, 30 of the reported deaths received preliminary listing as "may have been due to natural causes." Later, autopsies increased this figure to 62. The inability to determine whether physiological conditions caused the accident or the accident aggravated the existing condition may have restricted additions to this figure.

From this small sample, plus logic, it would appear that existing and induced physiological conditions of drivers involved in fatal automobile accidents may constitute a major portion of the true causes of death in an automobile. Our logic may be based on scrutiny of the actual time spent in automobiles. A total of 1.5 billion hours—200 hours per driver per year or approximately 3% of total time of each driver—is spent in an automobile in California. If 3% of the natural deaths due to chronic disease should occur during this time span, the number would approximate 1,350 deaths. This argument, while logical, will not allow a conclusion, because there are factors which have not been evaluated. However, the sample, plus logic, does indicate that it is necessary to attempt to lessen the influence of physiological conditions of drivers in automobile deaths.

Responsibility of the Medical Profession

It is my opinion that the most effective approach to this is through active, planned use of methods available only to the medical profession. It is also my opinion that the medical profession is presently unaware of the significance of this aspect of the problem and consequently is not taking active or planned curative action.

For example: how many doctors, when diagnosing hypertension, recommend relaxation through an automobile trip down crowded highways? How many depressant or stimulating drugs are administered without restriction being placed on the patient's driving? How many patients with cardiac problems are cautioned about the strain involved in driving at high speeds on crowded freeways? How many persons suffering from diabetes are, because of sugar imbalance, exposing other motorists and themselves to destruction?

Another small sampling was recently conducted which may lead to an inference in this regard. One hundred convicted drunken drivers were asked if they had discussed with a physician their problem of drinking and driving. Out of the 100, only 7 had discussed with a doctor their excessive drinking and, in these 7 instances, the problem of their drinking as it affected their driving was not mentioned.

Conclusions

The preceding information results in the following conclusions: The most effective method of treatment of the problem of automobile deaths and injuries is attacking the basic causes, thereby effecting a reduction in the number of accidents. Basic causes are existing mental and physiological conditions of drivers which dictate such behavior as speeding or reckless driving. Planned action cannot be effectively taken unless facts are gathered by joint research teams composed of representatives of the medical profession and existing accident-prevention agencies. Unless these steps are taken, 10 years from today we will have investigated and analyzed 15 million more accidents and still be forced to admit that we know very little about the basic causes of those accidents.

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INFLUENCE OF CHLOROTHIAZIDE ON WATER AND ELECTROLYTE EXCRETION IN PREECLAMPSIA

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The mechanism of the diuresis provoked by chlorothiazide was studied in 14 women hospitalized for toxemia of pregnancy. They received 500 mg. of chlorothiazide orally twice a day in addition to a well-established basic treatment for toxemia, and the results were compared with those in a group of 23 patients who received the basic treatment without the chlorothiazide. It was also possible to compare two-day periods in which the drug was given with two-day periods in which it was withheld. While the drug did not cause any consistent changes in the urinary pH, titratable acidity, mean urinary ammonia level, serum carbon dioxide content, serum sodium level, serum potassium level, serum chloride level, or patient's body weight, it did cause a marked increase in the urinary excretion of sodium, potassium, and chloride. Chlorothiazide in vitro strongly inhibits carbonic anhydrase, but its action under the conditions described in patients with preeclampsia differed from that of other carbonic anhydrase-inhibiting diuretics and also from that of mercurial diuretics.

It has long been a goal of research scientists to develop a diuretic drug which would be effective on oral administration and which would not produce serious electrolyte imbalance. Recently, chlorothiazide (Diuril), a new diuretic agent, has shown considerable promise in animal experiments. Chemically, chlorothiazide is 6-chloro-7-sulfamyl-1, 2, 4-benzothiadiazine-1, 1-dioxide.[1] Its structure is represented in figure 1. This compound is structurally related to some carbonic anhydrase-inhibiting diuretics, in that it contains a sulfamyl group attached to a benzene ring.

Preclinical experiments indicate that this compound possesses a high degree of activity as an inhibitor of carbonic anhydrase in vitro.[2] It is considered to be about 10 to 30 times as potent as sulfanilamide in this respect. In animals, chlorothiazide causes a marked increase in the urinary excretion of sodium, potassium, chloride, and water.[3] Excreted sodium is matched approximately mol for mol by chloride ions.[2] This effect is similar to that of mercurial diuretics, although chlorothiazide does not contain mercury. At high doses, bicarbonate excretion takes place, presumably because of inhibition of carbonic anhydrase. Because chlorothiazide is an effective diuretic in dogs at doses which do not produce bicarbonate excretion, these animal experiments suggest that its mechanism of action cannot be explained on the basis of carbonic anhydrase inhibition. Since the mechanism of this agent is still doubtful, we were particularly interested to investigate both the clinical effectiveness and the mechanism of action of chlorothiazide in some of the abnormalities of human pregnancy.

Materials and Methods

All patients diagnosed as having toxemia of pregnancy who were admitted to the obstetrics and gynecology service of King County Hospital during a period limited to the study of chlorothiazide were included in this study, with the exception of those patients who left the hospital against medical advice before the experimental period had elapsed. All patients were hospitalized during the period of investigation. The final diagnosis of toxemia was based on information obtained during the antepartum period, the period of hospitalization, and the follow-up period, at least three months post partum. The series consisted of a total of 14 women, 9 Caucasian, 3 Negro, and 2 American Indian, who were investigated during the immediate postpartum period in the hospital. This group of patients lent itself to comparison with another group of similar patients with toxemia of pregnancy previously studied in the same manner, with the exception that no diuretic drug was administered. In this controlled study of hospitalized patients we were able to investigate extensively many factors bearing on the course of toxemia of pregnancy and to analyze the effect of chlorothiazide in modifying those factors.

Each patient was studied over a seven-day period. Bed rest was enforced for the first three days, after which the majority of patients were made ambulant. A food intake consisting of a 1,200-calorie, neutral-ash, low-salt diet, containing approximately 30 mEq. of sodium daily, was maintained unless the patient was unable to tolerate oral feedings, in which case intravenous feedings were

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carried out. Food trays were weighed before and after each meal, and the actual daily intake of sodium, calories, acid, and basic ash was calculated. Sedation in varying degrees depending on the severity of the toxemia was prescribed as appropriate. All urine was collected as 24-hour specimens and kept under 25 ml. of mineral oil in order to prevent alterations in chemical values because of exposure to air. To prevent contamination by lochia, the urine from all postpartum patients was collected through indwelling Foley catheters.

The foregoing general measures constitute the general toxemia regimen of the department of obstetrics and gynecology of the University of Washington and have been kept constant for several years. The only modification from the usual program was the addition of 500 mg. of chlorothiazide given orally twice a day in the experimental group. Patients in the control group received no diuretic agents. During the first 24 hours of hospitalization no chlorothiazide was administered. On the second and third postpartum days, 500 mg. of chlorothiazide was given twice daily. During the fourth and fifth postpartum days, no chlorothiazide was given. On the sixth and seventh days the drug was again administered in the same dosage.

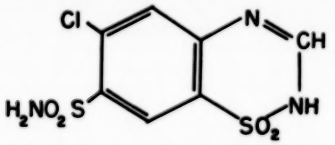

Fig. 1.—Chemical structure of chlorothiazide.

Serum sodium, potassium, and chloride levels were determined daily. On the second, fourth, and sixth hospital days blood urea nitrogen level, total protein level, albumin-globulin ratio, and fibrinogen and serum carbon dioxide levels were measured. On each of the daily 24-hour urine samples, urine pH, total volume, albumin level, specific gravity, ammonia content, titratable acidity, and sodium, potassium, and chloride levels were determined. The weight of each patient in grams was determined daily at the same time by the same person on a specially constructed scale for bedside weighing. The weights were accurate to 10 Gm. Blood pressure and edema were evaluated daily by the same person.

Sodium and potassium levels were determined by a flame photometer method with use of the Baird spectrophotometer. The chloride level was determined by the method of Schales and Schales,[4] blood urea nitrogen level by a slight modification of the method of Van Slyke and Cope,[5] carbon dioxide content by a slight modification of the method of Van Slyke and Neill,[6] titratable acidity by the method outlined by Hawk and co-workers,[7] ammonia by a slight modification of the method of Van Slyke and Cullen,[8] and pH with the Beckman, model G, pH meter.

All data were submitted to statistical analysis to determine the effect of chlorothiazide on the course of toxemia of pregnancy in the postpartum period. Since most reports attach great significance to the day-to-day changes occurring after the administration of a given drug, we considered it highly important to determine whether such changes would occur in a group of patients similarly treated except for the use of the drug. The fact that untreated patients may exhibit statistically significant changes from day to day makes it imperative that observations be made in a control group if the effect of a drug is to be properly evaluated. It is incorrect to ascribe to the action of a drug the finding of a significant difference until control studies have been performed. The failure to observe this principle has led to much confusion and misinformation in the past.

The Student's *t* test[9] was used to compare means in the chlorothiazide and control groups on a day-for-day basis. The reproducibility of the individual determinations was considered in establishing the p values on levels thought to be significant. In general, those observations having a low coefficient of variation, such as on the serum electrolytes, were considered significant at a level of $p=0.01$. For observations having a high coefficient of variation, as on the urine electrolytes and weight gain, the level of significance was established at $p=0.05$.

Results

The results obtained in this study in the 14 postpartum patients with toxemia of pregnancy who were treated with chlorothiazide are summarized in table 1. The results obtained in the group of 23 patients with toxemia of pregnancy studied in the postpartum period who did not receive any diuretic drugs are summarized in table 2. The latter group will be referred to as the control group.

Urine Sodium.—As shown in table 1, the urine sodium excretion remained constant during the first three days, being 73.2 mEq. per 24 hours the first (no drug) day and 70.7 and 75.9 on the second and third postpartum days, which were the first two days that the drug was given. Thus, the patients treated with chlorothiazide did not experience the drop in sodium excretion that the control group did (fig. 2). Significant increases of sodium excretion were found on the second day of the first course of drug administration (control group 47.3 mEq. per 24 hours, chlorothiazide group 75.9 mEq. per 24 hours: $p=0.05$) and on both days of the second course (control group 23.6 mEq. per 24 hours, chlorothiazide group 59.7 mEq. per 24 hours: p=

0.002; control group 28.0 mEq. per 24 hours, chlorothiazide group 66.2 mEq. per 24 hours: p=0.005). On the fourth and fifth days, on which no drug was given, the chlorothiazide group excreted significantly less sodium than the control group (control group 59.1 mEq. per 24 hours, chlorothiazide group 31.6 mEq. per 24 hours: p=0.04; control group 42.6 mEq. per 24 hours, chlorothiazide group 28.9 mEq. per 24 hours: p=0.05). The level of significance for this determination was established at p=0.05.

Urine Potassium.—In the chlorothiazide group the urine potassium excretion increased during the administration of chlorothiazide and decreased when the drug was withdrawn. In general, the changes were more pronounced quantitatively than those of urine sodium excretion. When the chlorothiazide group was compared to the control group it was found that, in contrast to findings on urine sodium, a statistically significant increase in excretion of urinary potassium occurred on each day of both the first drug period (control group 56.2 mEq. per 24 hours, chlorothiazide group 89.3 mEq. per 24 hours: p=0.004; control group 50.0 mEq. per 24 hours, chlorothiazide group 92.8 mEq. per 24 hours: p=<0.001) and the second drug period (control group 54.5 mEq. per 24 hours, chlorothiazide group 81.9 mEq. per 24 hours: p=0.005; control group 45.9 mEq. per 24 hours, chlorothiazide group 90.4 mEq. per 24 hours: p=0.001), as illustrated in figure 3. The statistical level of significance for this determination was established at p=0.05.

Urine Chloride.—Mean urine chloride excretion rose sharply from that of the control group during the first course of chlorothiazide therapy, as shown in figure 4 (first drug day: control group 77.4 mEq. per 24 hours, chlorothiazide group 129.1 mEq. per 24 hours: p=0.007, second drug day: control group 51.0 mEq. per 24 hours, chlorothiazide group 107.4 mEq. per 24 hours: p=<0.001). The chloride excretion rose from 52.9 mEq. per 24 hours on the first (no drug) day to 129.1 mEq. per 24 hours on the first day of drug administration. As was also noted for the urine sodium excretion, the excretion rate of chloride fell below the control values on the rest days (days four and five) after the first course of chlorothiazide therapy. This decrease was statistically significant on the fifth day (fourth day: control group 50.5 mEq. per 24 hours, chlorothiazide group 33.3 mEq. per 24 hours: p=0.10; fifth day: control group 47.7 mEq. per 24 hours, chlorothiazide group 25.1 mEq. per 24 hours: p=0.005).

TABLE 1.—*Data in Postpartum Patients with Toxemia of Pregnancy Treated with Chlorothiazide*

	Day of Treatment*																			
	1			2†			3†			4			5			6†			7†		
	No.	Mean	S.D.	No.	Mean	S.D.	No.	Mean	S.D.	No.	Mean	S.D.	No.	Mean	S.D.	No.	Mean	S.D.	No.	Mean	S.D.
Sodium excretion, mEq./24 hr.	10	73.2	61.6	9	70.7	44.9	10	75.9	32.1	9	31.6	28.8	10	28.9	24.4	10	59.7	34.5	10	66.2	40.7
Potassium excretion, mEq./24 hr.	10	58.4	15.0	11	89.3	37.8	12	92.8	23.0	10	64.2	23.8	12	69.1	24.0	10	81.9	26.2	10	90.4	33.0
Chloride excretion, mEq./24 hr.	9	52.9	58.7	11	129.1	74.1	12	107.4	75.4	10	33.3	21.1	11	25.1	20.5	10	53.2	39.4	10	59.2	32.0
Serum sodium level, mEq./liter	..	...	...	10	136.2	2.78	12	135.5	3.47	12	135.3	3.82	11	138.2	2.71	10	137.2	3.08	10	136.2	2.93
Serum potassium level, mEq./liter	..	...	...	11	4.59	0.693	12	4.38	0.373	12	4.49	0.485	12	4.44	0.513	10	4.75	0.630	10	4.45	0.492
Serum chloride level, mEq./liter	..	...	...	11	101.1	3.67	11	98.0	2.64	12	97.7	3.60	12	97.7	3.93	10	99.1	3.92	10	97.4	1.98
Weight loss, kg./24 hr.	..	...	...	10	0.577	0.61	11	0.55	0.50	12	1.25	1.38	11	0.08	0.08	9	0.562	0.38	9	0.50	0.41
Urine titratable acidity, mEq./24 hr.	10	30.3	10.2	11	58.6	13.4	12	27.7	8.0	12	30.1	13.9	12	29.4	15.7	10	24.7	9.1	10	29.0	13.8
Urine ammonia level, mEq./24 hr.	8	46.9	16.8	11	57.4	34.3	12	71.0	37.6	12	57.4	23.2	11	73.2	20.3	8	55.5	14.0	10	83.2	42.0
Urine pH	10	6.11	0.66	11	6.40	0.50	12	6.40	0.30	12	6.24	0.49	12	6.24	0.85	10	6.40	0.48	10	6.27	0.84
Serum carbon dioxide content, mEq./liter	..	...	...	10	23.1‡	3.6	..	...	...	11	23.3	4.4	..	...	...	9	24.3‡	3.6	..	...	...

* No.=number of patients; S.D.=standard deviation.
† Chlorothiazide, 1,000 mg.
‡ Determined prior to drug administration.

TABLE 2.—*Data in Postpartum Patients with Toxemia of Pregnancy Not Treated with Chlorothiazide*

	Day*																			
	1			2			3			4			5			6			7		
	No.	Mean	S.D.	No.	Mean	S.D.	No.	Mean	S.D.	No.	Mean	S.D.	No.	Mean	S.D.	No.	Mean	S.D.	No.	Mean	S.D.
Sodium excretion, mEq./24 hr.	18	97.8	55.2	23	69.2	44.0	23	47.3	29.2	22	50.1	40.0	20	42.6	18.4	17	53.6	19.8	15	58.0	12.4
Potassium excretion, mEq./24 hr.	18	61.5‡	44.1	23	56.2	28.5	23	50.0	14.9	23	54.7	47.6	18	69.6	27.4	14	54.5	20.3	14	45.9	21.1
Chloride excretion, mEq./24 hr.	17	124.0	85.6	19	77.4	31.6	23	51.0	25.8	23	30.5	36.1	19	47.7	21.5	15	43.8	28.4	15	35.8	21.0
Serum sodium level, mEq./liter	23	140.2	5.66	17	139.5	5.93	20	137.7	5.50	19	141.2	4.84	21	141.0	5.96	18	140.7	5.85	17	142.6	5.01
Serum potassium level, mEq./liter	22	4.27	0.385	19	4.37	0.510	20	4.38	0.503	19	4.56	0.746	21	4.49	0.695	17	4.31	0.675	18	4.50	0.576
Serum chloride level, mEq./24 hr	20	101.5	1.71	20	99.5	5.49	20	97.8	7.05	18	98.1	7.70	22	98.4	5.72	17	99.0	4.94	17	101.9	7.63
Weight loss, kg./24 hr.	..	...	...	17	0.79	1.03	19	0.54	1.05	21	0.55	0.77	21	0.59	0.64	21	0.53	0.60	23	0.64	0.69

* No.=number of patients; S.D.=standard deviation.

During the second course of chlorothiazide therapy the chloride excretion rate was markedly reduced and was significantly increased from that of the control group only on the second, or seventh postpartum, day (control 35.8 mEq. per 24 hours, chlorothiazide group 59.2 mEq. per 24 hours: p=0.02). The statistical level of significance for this determination was established at p=0.05.

Urine pH.—The urine pH showed no consistent pattern of change. The lowest mean value was 6.11 and the highest 6.40. No significant changes from day to day in mean pH were detected. In fact, on each day certain patients' urine pH went up slightly while that of other patients went down slightly. The level of significance for this determination was set at p=0.01.

Titratable Acidity.—Urinary titratable acidity varied from 27.7 mEq. per 24 hours to 30.3 mEq. per 24 hours during the seven days of observation.

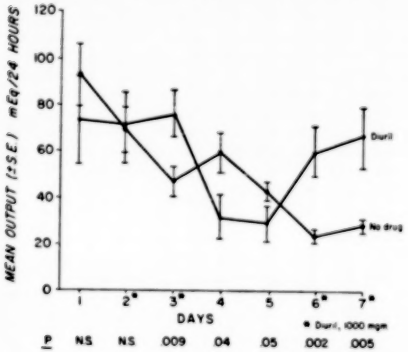

Fig. 2.—Increased urine sodium excretion in postpartum patients with toxemia of pregnancy treated with chlorothiazide over that of similar patients given no drug.

With the level of significance set at p=0.01, no significant differences from day to day in mean titratable acidity were noted. As in the pH determination, some patients had slight increases in titratable acidity and others slight decreases on the same day. No consistent pattern of titratable acidity change with drug administration could be made out.

Urine Ammonia.—Mean urine ammonia level varied from 46.9 mEq. per 24 hours to 83.2 mEq. per 24 hours during the seven days of observation. With the level of significance set at p=0.01, no significant differences from day to day were noted. On the second day (first drug day) and the fifth day (second day of the rest period), increases in urine ammonia levels which might be labeled "almost significant" occurred (first drug day p=0.02; second rest day p=0.03). Since these increases in urine ammonia levels were observed both when the drug was given (second day) and when the drug was withheld (fifth day), it is difficult to attach much importance to this finding. On neither of these days was enough change seen to be considered statistically significant, and, therefore, we ascribe the changes on the first drug day and the second rest day to chance.

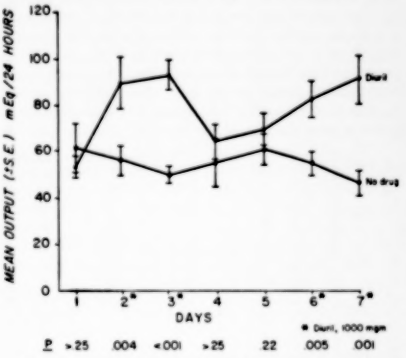

Fig. 3.—Increased potassium urine excretion in postpartum patients with toxemia of pregnancy treated with chlorothiazide over that of similar patients given no drug.

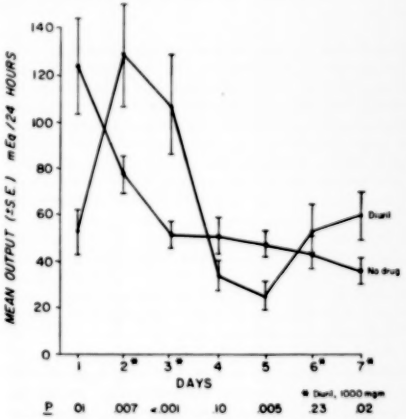

Fig. 4.—Increased urine chloride excretion, on three of four days that chlorothiazide was given, in postpartum patients with toxemia of pregnancy.

Serum Carbon Dioxide.—The serum carbon dioxide content did not change significantly from day to day during the administration of chlorothiazide.

Mean values were 23.1, 23.3, and 24.3 mEq. per liter respectively. The statistical level of significance for this determination was set at p=0.01.

Serum Sodium.—The mean serum sodium values for the chlorothiazide group and the control group are shown in figure 5. It is seen that on the second day of drug administration essentially no change in serum sodium levels occurred. The mean value for the chlorothiazide group was 135.5 mEq. per liter on the first drug day, changing to 135.3 mEq. per liter on the second drug day (the third day of

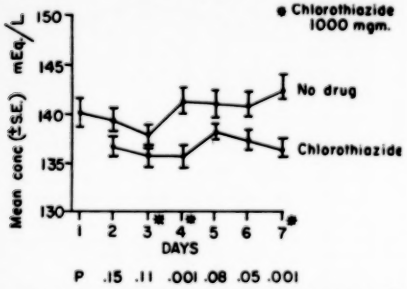

Fig. 5.—Serum sodium levels in postpartum patients with toxemia of pregnancy. Since blood specimens were obtained on days two and six before drug was administered, effect of chlorothiazide on serum sodium is reflected in values for days three, four, and seven. Note that mean serum sodium level of chlorothiazide group was not elevated on days four and seven.

observation). The control group, however, experienced an increase on the corresponding day from 137.7 to 141.2 mEq. per liter. The change in serum sodium levels exhibited by the control group constituted a significant difference, compared to the change exhibited by the chlorothiazide group (p=0.001). Thus, on the second day of drug administration the serum sodium levels in the drug group were not seen to have the same increase as in the control group. Similarly, on the second day of administration of chlorothiazide in the second course of therapy the chlorothiazide group did not show a corresponding elevation of serum sodium levels when compared with the control group (control 142.6 mEq. per liter, chlorothiazide group 136.2 mEq. per liter: p=0.001).

Serum Potassium.—The mean serum potassium level varied from a low of 4.38 to a high of 4.75 mEq. per liter during the seven-day period of observation. No statistically significant variation in the serum potassium level was detected through the course of this study. The statistical level of significance for this determination was set at p=0.01.

Serum Chloride.—The serum chloride level varied from a low of 97.4 mEq. per liter to a high of 101.1 mEq. per liter. The statistical level of significance for this determination was set at p=0.01. No significant changes in the level of serum chloride were found.

Patients' Weight.—Weight changes of the chlorothiazide patients were not impressive when compared with those of the control group (fig. 6). The only day in which the drug group lost significantly more weight than the control group was on the second drug day (control 0.55 kg. [1⅛ lb.], chlorothiazide group 1.25 kg. [3 lb.]: p=0.04). On the following day (the first rest day) the control group lost significantly more than the drug group (control 0.59 [1¼ lb.], chlorothiazide group 0.08 kg. [⅛ lb.]: p=0.025). While the average for all patients in the drug group was a net loss in weight each day, there actually were several cases in which patients gained weight while receiving chlorothiazide.

Toxicity.—In one patient who had bleeding during the third trimester, administration of the initial dose of chlorothiazide was followed by shock with increased pulse rate, decreased blood pressure, and pronounced diaphoresis. After blood transfusion, the patient improved; on subsequent delivery a partial abruption of the placenta was demonstrated. It is believed that her symptoms of shock could be considered as secondary to the abruption of the placenta and not secondary to the administration of chlorothiazide. No definitely related instances of toxicity of any sort were noted during the course of the study.

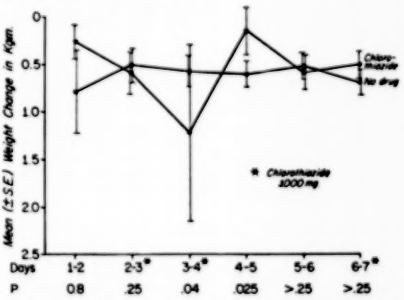

Fig. 6.—Weight change in chlorothiazide and control groups, showing loss of approximately same amount of weight during period of investigation.

Comment

Chlorothiazide, when administered in the postpartum period to patients with toxemia of pregnancy in doses of 500 mg. twice a day, produced the following effects:

The urinary excretion of sodium, potassium, and chloride was markedly increased. Urine pH, titratable acidity, and ammonia levels were not changed significantly.

Serum chloride, potassium, and carbon dioxide levels were not significantly altered. The serum sodium level of these patients failed to show the control pattern of increase when chlorothiazide was given.

It is interesting that the chlorothiazide group excreted significantly less sodium in the urine than the control group during the fourth and fifth days of the study, on which no chlorothiazide was given. While one might have expected the urine sodium level to drop to the control level when chlorothiazide therapy was discontinued, it does seem surprising that the level of sodium excretion should actually drop below that of the control group. The mechanism of such a change is not clear, especially in view of the finding that the serum sodium level was not altered significantly during this period. One might postulate that, since the drug group lost more sodium early in the experimental period because of the administration of chlorothiazide, an increased reabsorption of sodium occurred when the drug was withdrawn. The exact mechanism through which this increased reabsorption was accomplished remains to be determined. If chlorothiazide acts by blocking a normal renal mechanism for sodium reabsorption, the withdrawal of the drug could permit the "unblocking" of that mechanism with a subsequent decrease in urine sodium excretion. When the experimental group was compared with the control group, the urine potassium level was significantly increased during each day of drug administration.

It now seems well established that almost all of the potassium found in the urine results from an exchange with sodium in the distal convoluted tubule. Apparently that potassium which is filtered through the glomerulus is almost entirely reabsorbed in the proximal tubule. It follows, therefore, that any process which increases the sodium concentration in the distal tubule will enhance the excretion of potassium. In the distal tubule, both potassium and hydrogen ions within the tubule cell are exchanged for tubular sodium. Therefore, a process reducing the available hydrogen ion within the tubule cell would enhance potassium excretion, as occurs with carbonic anhydrase inhibitors. One can see that potassium excretion is affected by several varying processes; therefore, it is difficult to draw conclusions as to possible mechanisms of drug action from changes in the level of urine potassium.

The acidification of urine is dependent on the enzyme carbonic anhydrase. Its mechanism of action may be depicted as follows: In the renal tubule cells carbon dioxide from internal metabolism is combined with water to form carbonic acid which dissociates into hydrogen ions and bicarbonate ions. The hydrogen ions then pass across the cell membrane into the lumen of the tubule where they replace basic ions (for example, sodium) in the urine. This mechanism results in a conservation of the fixed basic ions of the body and in their replacement by hydrogen ions in the urine (fig. 7).

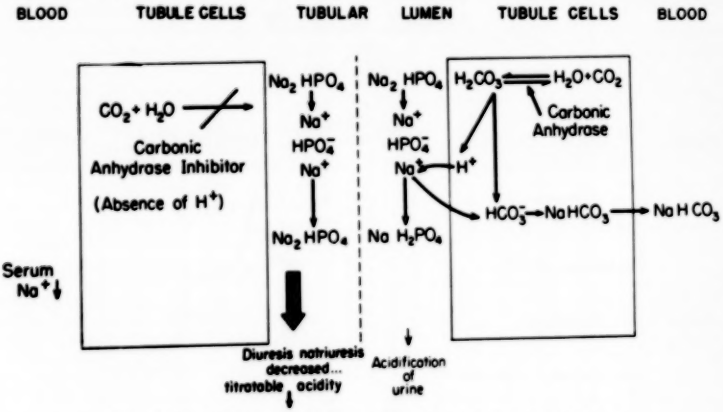

Fig. 7.—How inhibition of carbonic anhydrase decreases urine acidification.

The urine pH may be considered as a measure of carbonic anhydrase activity in the kidney. As urinary acidification occurs, the pH of the urine should decrease. Therefore, a carbonic anhydrase inhibitor should cause an increase in the urine pH, because it reduces urinary acidification by blocking the formation of carbonic acid from carbon dioxide

in the tubule cell. In animal experiments[10] no instance of the pH rising above 7.0 was observed when single doses of chlorothiazide were given. It has been reported[11] that large doses of chlorothiazide in man cause an increase in urinary pH but as dosage is reduced the urine becomes more acid, because the chloruretic effect persists in the face of a decreased bicarbonate excreting power. In some of our patients, the urine was alkaline. However, no statistically significant change in urine pH was demonstrated. This is an indication that, in the clinically effective doses used in this study, no measurable carbonic anhydrase inhibitory activity is detectable.

If chlorothiazide is an effective inhibitor of carbonic anhydrase activity, one would expect the titratable acidity to fall during the administration of the drug and to rise after its withdrawal, as is observed with classic carbonic anhydrase inhibitors. No such change was detected, indicating that carbonic anhydrase inhibition did not occur in our patients.

The measurement of urine ammonia level provides another indication of carbonic anhydrase activity. Glutamine is acted on in the renal tubule cell to give glutamic acid, plus ammonia, through the action of the enzyme glutaminase. The ammonia combines with hydrogen ions from the carbonic acid reaction to produce ammonium ions, which diffuse into the urine and replace basic cations (fig. 8).Of course, the urine ammonia determination may not be considered as specific a test for carbonic anhydrase function as those for pH and titratable acidity because, in addition to depending on available hydrogen ions, the urine ammonia level also depends on a functioning glutaminase and on urine pH. As the patient's nitrogen intake is held relatively constant, inhibition of carbonic anhydrase by chlorothiazide should be reflected by decreased urine ammonia levels during periods of drug administration. No such decrease was observed. The observation that there was no significant change in urine ammonia levels may be interpreted best as an indication that no dysfunction of either the glutaminase or carbonic anhydrase systems occurred as a result of chlorothiazide therapy. This agrees with and lends support to the finding that there is no significant change in titratable acidity and pH and is strong evidence that no inhibition of carbonic anhydrase activity occurred in our patients.

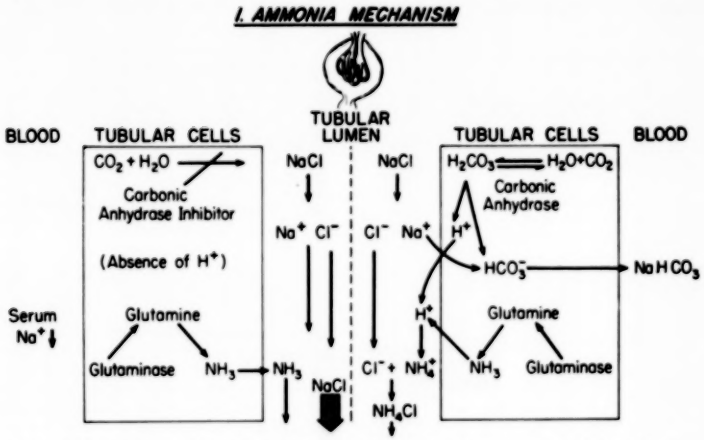

Fig. 8.—Interaction of carbonic anhydrase and glutaminase systems in reabsorption of urine sodium.

The carbon dioxide content did not change significantly during the administration of chlorothiazide. The classic carbonic anhydrase inhibitor type of diuretic produces a state of metabolic acidosis after a day or two of administration. This may be explained on the basis of the electrolyte excretion pattern. Thus, sodium, potassium, and bicarbonate are excreted in large amounts, while almost no hydrogen ion is excreted. This means that there is a net loss of basic cations (sodium and potassium) with the production of hyponatremic, hypokalemic, metabolic acidosis. The serum carbon dioxide level is, therefore, markedly reduced.

The fact that no significant reduction in serum carbon dioxide content was observed indicates that

acidosis was not evident in our patients with the doses used in our study. This observation provides evidence that carbonic anhydrase inhibition does not explain the mechanism of action of chlorothiazide. Neither is this action similar to that of mercurial diuretics. These agents characteristically cause hypochloremic metabolic alkalosis with a compensatory increase in serum carbon dioxide level. In its effects on serum carbon dioxide, chlorothiazide differs from both of these groups of diuretics.

Some cardiac patients have been reported to exhibit signs and symptoms of low serum sodium levels after administration of chlorothiazide.[10] This was observed in one of our patients with chronic renal disease, diagnosed as diabetic glomerulosclerosis after renal biopsy. No other patient exhibited an unusually low serum sodium level.

Comparison of Chlorothiazide with Carbonic Anhydrase Inhibitors.—When compared with carbonic anhydrase inhibitors, chlorothiazide exhibits striking differences, as shown in figure 9. Carbonic anhydrase inhibitors characteristically produce an increase in urine pH and a decrease in urine titratable acidity and ammonia level. These changes were not observed during the administration of chlorothiazide. Chlorothiazide is similar to carbonic anhydrase inhibitors in that both agents produce increased urinary excretion of sodium and potassium. While carbonic anhydrase inhibitors cause little change in chloride excretion, chlorothiazide results in a markedly increased excretion of chloride. Carbonic anhydrase inhibitors tend to lower serum sodium and potassium levels. This did not occur in the chlorothiazide group. However, a rise in serum sodium level which occurred in our untreated, control patients did not occur in the chlorothiazide group. Finally, carbonic anhydrase inhibitors cause metabolic acidosis, as determined by low serum carbon dioxide content; in our hands chlorothiazide caused no acid-base imbalance, and the serum carbon dioxide content was not significantly changed. At the doses used the carbonic anhydrase inhibitory properties of chlorothiazide demonstrable in vitro were not observed in vivo.

Animal experiments reported by Ford and others [11] have indicated that the diuresis mechanism of chlorothiazide is different from that of the classic carbonic anhydrase inhibitor acetazolamide. Apparently, the carbonic anhydrase-inhibiting properties which are demonstrable in vitro are not responsible for the diuretic effect, for, unlike acetazolamide, chlorothiazide causes (in animals) the excretion of similar amounts of sodium and chloride. It does not result in acidosis and does not lose its effectiveness if given on successive days. In general, our results in women with toxemia of pregnancy confirm those found by Ford and Spurr in their animal experiments.

It is important to consider that the statements made about lack of carbonic anhydrase inhibition apply to the dosage schedule used in our study. Perhaps at a higher dosage level or with prolongation of administration carbonic anhydrase inhibition might manifest itself, causing a much different excretion of electrolytes.

Additional evidence for a different mechanism of action between chlorothiazide and carbonic anhydrase inhibitors is provided by the studies of Finnerty and associates [12] on patients with toxemia of pregnancy. Their results, based on weight losses without electrolyte studies in clinic outpatients, showed a potentiation of acetazolamide diuresis when chlorothiazide was administered. The foregoing evidence, both from the literature and from our own studies, seems to indicate conclusively that chlorothiazide acts through some mechanism other than inhibition of the enzyme carbonic anhydrase.

	NON-PREGNANT			TOXEMIA OF PREGNANCY			
				CHLOROTHIAZIDE			
				1st Course		2nd Course	
	C.A.I.	Hg	Cl ⊖	1st day	2nd day	1st day	2nd day
Urine Na	↓	↓↓	↓↓	—	↓↓	↓↓	↓↓
" K	↓↓	—	↓↓	↓↓	↓↓	↓↓	↓↓
" Cl	—	↓↓	↓↓	↓↓	↓↓	—	↓
" pH	↓	↓ (?)	?	—	—	—	—
" TA	↓	↓ (?)	↓	—	—	—	—
" NH_3	↓	↓ (?)	↓	—	—	—	—
Serum CO_2	↓ (acidosis)	↓ (acidosis)	—		—		
" Na	↓	↓ or −	↓	—	? *	—	? *
" K	↓	—	↓	—	—	—	—
" Cl	—	↓	↓	—	—	—	—

Fig. 9.—Action of chlorothiazide in toxemia of pregnancy contrasted with that of carbonic anhydrase inhibitors, mercurial diuretics, and chlorothiazide in nonpregnant patients.

Comparison of Chlorothiazide with Mercurial Diuretics.—The electrolyte excretion pattern of sodium and chloride is qualitatively similar with both chlorothiazide and mercurials (fig. 9). Chlorothiazide causes a marked excretion of potassium, which is not observed with mercurials. In the serum, mercurials tend to cause hypochloremia with associated metabolic alkalosis and elevated serum carbon dioxide level. These serum changes were not observed with chlorothiazide.

While the electrolyte excretion pattern of chlorothiazide in the moderate doses used for this study somewhat resembles that of mercurial diuretics, Laragh [13] has cited several reasons to indicate that a different mechanism is involved. The activity of chlorothiazide is neither inhibited nor reversed by

dimercaprol. Conditions refractory to mercurials have responded to chlorothiazide, while those refractory to each drug given separately may respond to both drugs given simultaneously. The addition of a second drug for patients already receiving one agent often gives an increased diuresis. Steroid-induced edema is inhibited or reversed by chlorothiazide, while the mercurials are usually ineffective in such cases. Chlorothiazide is effective in hypochloremic alkalosis, while mercurials are not. The addition of ammonium chloride results in a potentiation of mercurial action, while chlorothiazide action is unaffected.

These facts, together with the differences in serum and urine electrolyte balances demonstrated in our study, provide good evidence that chlorothiazide has a different mechanism of action from mercurial diuretics.

Possible Mechanism of Chlorothiazide.—One explanation of the mechanism of chlorothiazide which accounts for the observations made in our study is that the drug in some way inhibits sodium reabsorption in the proximal renal tubule. This would result in the delivery of an increased amount of sodium into the distal renal tubule. The increased sodium level would provide more opportunity for potassium exchange in the distal tubule, leading to an increased excretion of potassium. Because not all of the extra sodium is replaced by potassium, the amount of sodium delivered into the urine would be increased also. Since it is believed that chloride ions follow sodium ions rather passively, with the blocking of sodium reabsorption in the proximal tubule, a larger amount of chloride would flow into the distal tubule. There is no known active mechanism affecting chloride ions in the distal tubule, and the increased amount of chloride is thought to pass into the urine in association with the increased sodium and potassium levels. Thus, increased excretion of sodium, potassium, and chloride could occur on the basis of a blocking of reabsorption of the single ion, sodium.

Conclusions

Chlorothiazide is a potent agent in promoting the excretion of sodium, potassium, and chloride from the body. When it was administered in a dosage of 500 mg. twice daily for two-day periods with a two-day rest period between each course of therapy, no serum electrolyte abnormalities were noted to occur. Despite the pronounced elevation of electrolyte excretion caused by chlorothiazide, patients with toxemia of pregnancy studied during the postpartum period did not lose weight at a significantly faster rate than patients not given the drug. Chlorothiazide is equally effective on readministration after a two-day rest period. No instances of toxicity or undesirable side-effects were noted.

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PATHOLOGICAL FINDINGS IN JAUNDICE ASSOCIATED WITH IPRONIAZID THERAPY

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Specimens of liver tissue were studied in 27 patients who had developed jaundice after taking iproniazid in amounts that totaled from 600 to 19,200 mg. over treatment periods ranging from 4 to 126 days. The aim was to define the type of hepatocellular damage associated with the jaundice and to account for the evident lack of relation between the dose of iproniazid and the severity of the hepatic lesions. The biopsy specimens showed severe spotty necrotic hepatitis with or without extensive necrosis: the 16 autopsy specimens showed either acute massive and submissive necrotic hepatitis or subacute hepatitis with massive and submassive collapse. Clinically, the findings were those of diffuse parenchymal liver disease, mostly without fever, commonly with hepatomegaly, and with terminal hepatic coma in the fatal cases. Results of conventional laboratory tests are tabulated. In some cases the jaundice appeared as late as 20 days after the cessation of therapy. Either the iproniazid activated existing subclinical viral hepatitis or else it was able to produce morphologic changes closely resembling those of viral hepatitis. In either case the possibility of inducing an insidious form of liver disease with high mortality should be kept in mind whenever the administration of iproniazid is found necessary.

The evaluation of injurious effects of drugs and chemicals on the liver is frequently difficult. Some of these, e. g., carbon tetrachloride, cause characteristic functional disturbances and structural alterations in the liver of all persons exposed to them. A close relationship between dose and extent of lesion exists, and the changes are reproducible in experimental animals. In contrast, some drugs produce hepatic injury only in some persons exposed to them—in fact, the percentage of those afflicted may be very small, the dose relation is not always evident, and the lesion cannot be produced in animals at will. In such instances, even if the hepatic injury is associated with jaundice, a causal relation between drug intake and liver damage has been recognized only after the observation of a considerable number of similar cases; the mechanism of this injury remains not established. Hepatic injuries of the cholestatic type, occurring after the administration of chlorpromazine, methyltestosterone, norethandrolone, or other drugs,[1] fall into this category.

Iproniazid (Marsilid) phosphate (1-isonicotinyl-2-isopropylhydrazine), an amine oxidase inhibitor initially used in the treatment of tuberculosis,[2] was recently found to be effective in alleviating various mental disorders, particularly depressions.[3] After the widespread use of iproniazid, reports of cases of jaundice have appeared [4] which developed after administration of this drug and may be related to it. The jaundice in iproniazid-treated patients is associated with biochemical evidence of significant hepatocellular injury and, in contrast to the cholestatic type of hepatic damage, the mortality is relatively high. To determine the type of injury and possible causal relation to drug intake, a study was made of the pathological features of biopsy and autopsy specimens of liver of patients who had developed jaundice after administration of iproniazid. An attempt was made to correlate these findings with the clinical manifestations of the hepatic disease and with the dosage of drug administered.

Material and Methods

The study comprised 13 biopsy specimens and 16 autopsy specimens obtained from 27 patients. Of the 23 patients on whom pertinent data are available, 16 were females and 7 males, and their ages ranged from 21 to 82 years. Ten patients were under 50 years of age; five patients each were in their sixth and seventh decades of life, and two patients and one patient in their eighth and ninth decades respectively (table 1). In one instance (case 19) two biopsy specimens were studied, of which the second specimen was taken three months after the first (or one month after subsidence of the jaundice), while in another (case 23) a biopsy and an autopsy specimen were examined which were obtained 23 days apart. Two biopsy and two autopsy specimens (cases 7, 14, 16, and 21) were from patients treated for jaundice at the Mount Sinai Hospital, New York, whereas most of the other specimens were supplied by other hospitals from all sections of the United States.

The clinical and laboratory data reported were secured by analysis of the entries made in questionnaires submitted by Hoffmann-LaRoche, Inc., to the clinicians who attended the patients included in the study. The findings in the biopsy and autopsy specimens of several patients who had received iproniazid, but did not develop jaundice and did not

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exhibit symptoms of liver disease, were not included in the study, since these specimens did not show structural abnormalities. Moreover, one patient, who under treatment with iproniazid developed jaundice which subsided and on whom a biopsy

TABLE 1.—*Clinical Data and Iproniazid Intake in Patients with Jaundice*

Case, No.	Age, Yr.	Sex	Total Iproniazid Dose, Mg.	Duration of Treatment, Days	Interval Between Appearance of Jaundice and Cessation of Therapy, Days*	Interval Between Appearance of Jaundice and Obtaining of Specimen, Days	Type of Specimen†
1	43	F	9,200	37	0	12	A
2	65	F	2,100	14	0	17	A
3	31	F	4,400	33	−12	12	A
4	57	F	3,150	31	3	11	A
5	21	M	600	4	2	33	B
6	32	M	19,200	118	0	12	A
7	58	F	2,200	26	−3	9	B
8	39	M	12,000	102	0	17	B
9	...	...	3,000	22	...	17	B
10	63	F	4,000	90	0	10	A
11	40	M	5,000	35	6	11	B
12	56	F	4,650	34	−30	13	B
13	29	F	4,500	55	0	10	A
14	71	F	3,050	63	−8	30	A
15	69	F	5,250	90	−6	29	A
16	74	F	1,000	42	0	30	B
17‡	52	F	1,850	10	0	5	B
18	36	F	2,350	44	0	24	B
19A	45	M	1,340	32	0	12	B
19B§	45	M	1,340	32	...	102	B
20	52	F	2,500	72	0	8	B
21	82	F	3,525	126	0	42	A
22	68	F	2,000+	60	0	32	A
23‖	...	...	...	...	...	...	A
24	...	...	1,800	50	...	7	A
25A	66	M	10,100	101	1	20	B
25B	66	M	10,100	101	...	53	A
26‖	...		...	...	...	...	A
27	69	M	11,000	60	0	11	A

* Negative figures indicate number of days medication was discontinued prior to appearance of jaundice.
† A—autopsy; B—biopsy.
‡ This patient died subsequently.
§ Repeat biopsy; jaundice had disappeared.
‖ Data not available.

was performed several months later, was omitted since hepatitis was not evident in the specimen examined. Hematoxylin-eosin stains and, in addition, where possible, reticulum impregnations and chromotrope/aniline blue stains were used to study the sections.

Results

The cases studied by either biopsy or autopsy can be divided, from the morphologic viewpoint, into several groups.

Biopsy Specimens.—The study of biopsy specimens resulted in a division of the cases into two main groups.

Severe Spotty Necrotic Hepatitis (Cases 9, 11, 12, 16, 17, and 19A): The liver cell plates were interrupted throughout the lobule by necrosis of single cells or small groups of liver cells which were replaced by aggregations of histiocytes and lymphocytes with a varying admixture of segmented leukocytes, some of which were eosinophilic (fig. 1*A*). The persisting liver cells varied greatly in size and staining qualities. Some were conspicuously enlarged and their cytoplasm was rarefied (ballooned cells); others were smaller and exhibited a dense cytoplasm, while a third type of cell had strongly acidophilic cytoplasm and a pyknotic or broken nucleus. These cells were often expelled from the liver cell plate and were seen as refractile globules in the tissue spaces (acidophilic bodies) (fig. 1*B*).

Other liver cells showed conspicuous evidence of regeneration. The variation in the appearance of the cells in the same area was the outstanding feature of the process. The Kupffer cells were mobilized and contained, as did intralobular macrophages, much brown lipofuscin pigment, apparently derived from liver cell breakdown. The sinus-

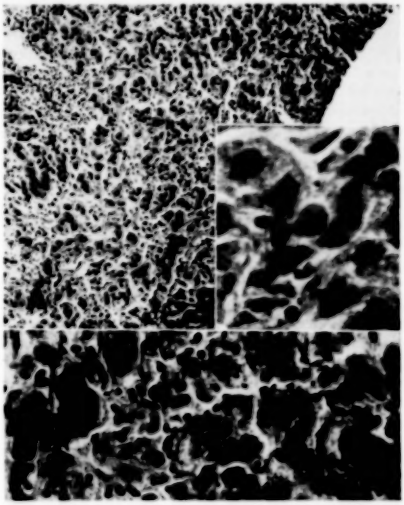

Fig. 1.—Photomicrographs of liver biopsy specimens of patients who developed jaundice after intake of iproniazid (hematoxylin and eosin stain). *A* (case 12), acute spotty necrotic hepatitis with severe interstitial and portal inflammation and regeneration of individual cells (120×). *B*, acidophilic body lying in tissue space containing pyknotic nucleus (*arrow*) (400×). *C*, interstitial accumulation of lymphocytes and macrophages containing lipofuscin around liver cells varying greatly in appearance and bordering on bile plugs in bile capillary (*arrow*) (240×).

oids were dilated in places but more often they were obstructed by protein debris intermixed with exudate cells. Many bile canaliculi were dilated and contained bile plugs (fig. 1*C*). Extracellular bile droplets were also seen. The thickened wall of the central vein frequently harbored similar exudate cells. The enlarged and edematous portal tracts

exhibited exudate cells—including lipofuscin and bile pigment carrying macrophages. The borders of the portal tracts were obscured by proliferation of ductules, some of which contained bile plugs and exudate cells in their irregularly widened lumens. The duration of jaundice up to the time of biopsy varied in these cases from 5 to 30 days. In one instance a second biopsy after subsidence of jaundice (case 19B) revealed only portal and periportal proliferation of ductules surrounded by fibrosis and exudate cells.

Severe Spotty Necrotic Hepatitis with Extensive Necrosis (cases 7, 20, and 23A): Extensive areas of necrosis were seen in addition to the changes described above. Particularly in the centrolobular zone, liver cells had disappeared from large contiguous areas, and the stroma was collapsed around the persisting mesenchymal elements (fig. 2A). In one patient (case 23A) who subsequently died with subacute hepatitis, the collapse involved whole lobules, the outlines of which were marked by periportal ductular proliferations. The accentuated liver cell breakdown was indicated in all these cases by a very heavy accumulation of lipofuscin both in the Kupffer cells and the macrophages. The jaundice had set in 8 to 30 days before the biopsy was done.

In one instance of mild spotty necrotic hepatitis (case 8), the lesions were similar to those in the first group except that the hepatocellular degeneration, necrosis, and inflammatory reaction were far less severe, although the jaundice was of similar duration. In a subsiding hepatitis (case 5), cellular degeneration and inflammatory lesions in the parenchyma were subdued, while the portal tracts still showed the same pathological picture described above. Lipofuscin pigmentation of the Kupffer cells and regeneratory processes of the liver cells were conspicuous. The total dose of iproniazid administered was the smallest and the duration of therapy the shortest in the entire group. However, this patient had been exposed to cases of jaundice, probably of infectious origin. This raises the question as to whether this patient might not have had infectious hepatitis.

In a case of subacute hepatitis (case 18), the centrolobular zone exhibited severe bile stasis, hepatocellular degeneration, and necrosis (fig. 2B), while in the intermediate zone regeneration with multinucleated giant cells and acidophilic bodies were noted. The portal tracts contained cellular exudate and were fibrotic and connected with each other, producing perilobular fibrosis. The patient had become jaundiced only 24 days before the biopsy was performed.

Autopsy Specimens.—A study of autopsy specimens resulted in a division of the cases into two main groups.

Acute Massive and Submassive Necrotic Hepatitis (cases 1, 3, 6, 10, 13, 24, 26, and 27): In large areas of the liver, all epithelial cells had disappeared in whole lobules or in large parts of them. The framework was either entirely collapsed or was kept still somewhat expanded by erythrocytes which were frequently pooled, or by a mixture of proliferated Kupffer cells with macrophages, both of which contained lipofuscin and occasionally bile pigment. These cells were interspersed to a varying degree with lymphocytes, plasma cells, and neutrophilic and eosinophilic segmented leukocytes (fig. 3A). The reticulum framework itself was intact even where closely approximated. Fragments of the preexisting lobules revealed liver cell plates with dense

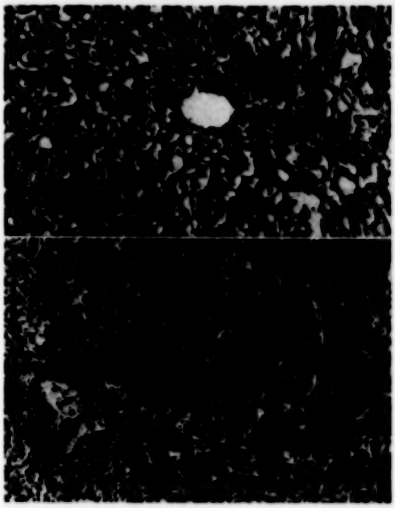

Fig. 2.—Photomicrographs of liver biopsy specimens of patients who developed jaundice after intake of iproniazid (hematoxylin and eosin stain). *A* (case 20), severe spotty necrotic hepatitis with extensive centrolobular necrosis and collapse of framework around central vein (*arrow*) (120×). *B*, (case 18), subacute hepatitis with bile stasis around central vein which exhibits inflammatory infiltration in its wall (*straight arrow*). Perilobular fibrosis (*curved arrow*) connects portal tracts (63×).

fat-free cytoplasm. Occasionally, beginning regeneration was indicated by formation of liver cell plates which were several cells thick. On the border of the preserved parts of the parenchyma, the liver cells disintegrated completely, passing through a stage of heavy vacuolization apparently produced by fat deposition; acidophilic bodies were also present. The acuity of the process was indicated by the absence of liver cell breakdown products.

Toward the periphery of the lobules many bile ductules, arranged in cords and plates, were lined by irregular epithelial cells which sometimes piled up, formed giant cells, and seemed to be derived from liver cells. The lumens of the ductules contained bile casts and protein-rich exudate intermixed with segmented leukocytes which, with other inflammatory cells, also accumulated around the ductules (fig. 3*B*). These ductular structures indicated the border of the otherwise deepithelialized, collapsed "ghost" lobules. Their center frequently exhibited a thickened hepatic vein branch infiltrated by exudate cells. This apparently fulminant type of hepatic necrosis was observed after 10 to 12 days of jaundice.

Fig. 3.—Photomicrographs of liver autopsy specimens of patients who developed jaundice after intake of iproniazid. *A* (case 3), fulminant type of massive necrotic hepatitis; collapse and accumulation of red blood cells in central and intermediary zone around hepatic vein branch exhibiting inflammatory infiltration (*arrow*), the periphery of the lobule marked by ductular proliferations (40×). *B*, proliferated ductules and scavenger cells (*straight arrow*) as well as vacuolated degenerating liver cells (*curved arrow*) (240×).

Subacute Hepatitis with Massive and Submassive Collapse (cases 2, 14, 15, 21, 22, and 25B): The lobular architecture, although basically almost always intact, was obscured by degeneration and necrosis, collapse, and regeneration. In the degenerated areas, the cytoplasm of the liver cells was irregular, clumped, bile-pigmented, and vacuolated. Acidophilic bodies were seen in some instances, and the mesenchymal response in three of these cases resembled somewhat that seen around the areas of spotty necrosis in the biopsy material. However, the degree of the inflammatory reaction was remarkably less than in comparable biopsy material. The accumulation of lipofuscin pigment was of equal degree. The collapsed areas usually involved the central zones as well as the immediate periportal area of the parenchyma.

In addition, slits of collapsed parenchyma produced septums linking central zones with each other as well as with portal tracts and dissected portions of the lobules (fig. 4). The collapse appeared recent since the wavy collagenous membranes of the collapsed zones in connective tissue stain were differentiated from the heavy connective tissue bundles of the preformed portal tracts. The isolated portions of the parenchyma exhibited conspicuous regeneration, with giant cells and plates that were two or more cells thick in places where there was still degeneration and necrosis as well as bile stasis. In some of these nodules, the liver cell plates were rearranged concentrically to present the typical regenerative nodules of cirrhosis. Bile ductules often connecting with liver cells were just as

Fig. 4 (case 21).—Photomicrograph of liver autopsy specimen of patient who developed jaundice after intake of iproniazid. Subacute hepatitis existed with submassive collapse, acute degeneration (*straight arrow*), and beginning nodular regeneration and bile stasis (*curved arrow*) (hematoxylin and eosin stain) (63×).

prevalent as in the acute group. Frequently their lumens appeared dilated by large dense microcalculi, and, in two instances, bile infarcts were present. The nodular transformation of the parenchyma represented transition into early postnecrotic cirrhosis, but in most instances broad areas of acute massive collapse were still present. Jaundice had been present from 17 to 53 days.

Two cases (cases 4 and 23), which were of shorter duration, presented a transition between both groups. In these specimens necrosis and collapse were observed in the centrolobular and periportal areas, while spotty necrotic changes were seen in the remainder of the parenchyma.

The results of some hepatic tests are available in 25 of the 27 patients (table 2). The total serum bilirubin level was elevated in all patients for whom findings were reported. In 11 of the fatal cases and in 5 of the nonfatal cases, the bilirubin values exceeded 15 mg. per 100 ml. of serum close to the time at which specimens for pathological examination were obtained. In one instance (case 2) the bilirubin value 10 days before death of the patient was almost three times that recorded preterminally. In five other fatal instances (cases 1, 3, 10, 13, and 25), bilirubin levels rose progressively. In five nonfatal cases (5, 7, 12, 16, and 19) records are available of the return of bilirubin levels, as

TABLE 2.—*Results of Hepatic Tests Done Close to Time of Biopsy or Death*

Case. No.	Type of Specimen*	Total Bilirubin Level, Mg. %	Cephalin Flocculation	Thymol Turbidity, Units	Serum Albumin Level, Gm. %	Serum Globulin Level, Gm. %	Serum Alkaline Phosphatase, Units†	Serum Glutamic Oxaloacetic Transaminase, Units
1	A	12.4	3+	...	3.1	2.6	6.0 B.U.	...
2	A	12.0	...	12.3	...	...	4.1 B.U.	213
3	A	27.0	...	...	...	...	...	...
4	A	2.2	...	...	...	...	...	...
5	B	2.1	neg.	2.9	...	...	4.4 K.A.U.	35
6	A	23.0	...	...	1.6	2.4	4.5 B.U.	...
7	B	21.4	2+	5.4	3.4	2.8	13.7 K.A.U.	100
8	B	12.0	4+	4.5	4.3	4.0	3.6 B.U.	...
9	B	...	4+	20.5	normal	normal	...	...
10	A	25.0	...	16.0	...	...	7.1 B.U.	910
11	B	20.2	4+	47.5	2.8	4.8	8.3 B.U.	...
12	B	12.5	3+	9.5	3.9	2.7	21.2 B.U.	540
13	A	17.4‡	neg.	16.5	...	...	7.0 B.U.	280
14	A	30.0	3+	5.7	3.5	4.0	22.2 K.A.U.	460
15	A	16.7	4+	6.4	...	...	8.4 B.U.	224
16	B	31.4	2+	...	3.0	4.6	15.8 K.A.U.	740
17	B§	13.4	4+	10.3	4.2	3.0	7.2 B.U.	...
18	B	7.4	4+	2.2	...	..	6.2 S.J.U.	1,350
19A	B	15.2	...	5.3	4.2	2.1	8.9 K.A.U.	640
19B	B	0.7	...	...	4.8	2.1	4.6 K.A.U.	22
20	B	31.2	2+	12.2	...	...	...	...
21	A	24.4	4+	7.8	2.3	3.4	16.9 K.A.U.	183
22	A	28.0	4+	23.0	...	...	7.9 B.U.	2,000
23	A	...	...	...	...	...	...	...
24	A	30.3	...	...	...	...	...	...
25A	B	23.4	4+	11.2	...	...	5.7 B.U.	720
25B	A	23.4	3+	11.0	...	...	4.8 B.U.	...
26	A	...	...	...	...	...	...	...
27	A	32.3	...	15.0	...	...	9.4 B.U.	80

* A = autopsy; B = biopsy.
† B.U. = Bodansky Units; K.A.U. = King-Armstrong Units; S.J.U. = Shinowara-Jones Units.
‡ Direct reading.
§ This patient died subsequently.
‖ Data not available.

Clinical and Laboratory Findings

The clinical manifestations of the four patients observed uniformly in one institution [4] and of the patients on whom pertinent information was obtained by questionnaires were those of diffuse parenchymal liver disease, mostly without fever. Hepatomegaly was present in a large number of cases. Sometimes the liver was tender and shrank in the preterminal period. To our knowledge, two of the patients studied by biopsy died subsequently (cases 17 and 25A). From the latter patient (case 25B) an autopsy specimen was also obtained. Hepatic coma seemed to have been present in all fatal cases.

well as of the abnormal findings in other hepatic tests, to normal as these patients recovered, except for prolonged elevation of sulfobromophthalein retention in case 19. At least in one instance (case 11) the bilirubin value remained above 20 mg. per 100 ml. for one month.

Cephalin flocculation was 3+ or 4+ in 12 of 17 patients for whom values were reported. Thymol turbidity, which was above 4 units in 16 of 20 patients, exceeded 15 units in 5 instances. The serum activity of alkaline phosphatase was outside the normal range in 16 of the 20 patients in whom results were available. The values of transaminase which were reported for 15 patients were all ele-

vated with the exception of that in one patient (case 5). However, in one instance, the elevated transaminase value decreased to within normal limits at the time of the second biopsy (case 19B). In three patients (cases 2, 13, and 27) transaminase values dropped precipitously before death. One patient (case 18), with a very high transaminase value, was known to have had jaundice about seven years ago. Significant aberrations of red and white blood cell counts were not reported in any of the cases.

Iproniazid Intake

The total amounts of iproniazid administered to the individual patients ranged from 600 to 19,200 mg. (table 1). In the fatal cases the average total dose, the average duration of medication, and the average daily dose per patient were 5,672 mg., 61.9 days, and 106.7 mg. respectively. In the nonfatal cases the corresponding figures were 3,484 mg., 47.4 days, and 80.5 mg. respectively. The difference in total iproniazid intake between fatal and nonfatal cases is statistically insignificant ($p < 0.3$).

In most instances, iproniazid therapy was discontinued on the onset of jaundice, but in a few patients drug administration was continued for a few days after the icterus had developed. Contrariwise, in one fatal case and in one nonfatal case, therapy was stopped 12 days and 20 days, respectively, prior to the development of jaundice. Moreover, one patient (case 4), who received an average daily dose of 102 mg. for 31 days, died, but another patient (case 8), who was given an average daily dose of 118 mg. for 102 days, survived.

Comment

The presented cases of fatal and nonfatal jaundice occurring after iproniazid therapy raise the following questions: 1. Are the hepatic lesions sufficiently uniform to indicate a single, well-defined disease process? 2. What is the basic pathology? 3. What is the relation between structural alterations of the liver and the clinical manifestations? 4. What is the relation between the iproniazid dose and the severity of the hepatic lesions. 5. What causal relationship between iproniazid administration and these lesions can be assumed?

When jaundice develops after administration of a drug or during the course of a disease, pathological study frequently uncovers a variety of lesions, some of which appear not related to the drug or the disease in question but rather have coincidental causes, e. g., biliary tract disease. In contrast, the cases described here represent a uniform pathological process which varies only in the severity and duration of the lesions. No morphologic evidence of a preexisting liver disease was found. Features predominant in the autopsy specimens were observed in the biopsy specimens and vice versa, suggesting transitional stages between fatal and nonfatal cases. Such stages are usually not as clear in other material of hepatitis.

Basically, the lesion may be described as a diffuse hepatocellular injury with associated inflammatory reaction and bile stasis. The lesion seems to proceed from single cell necrosis to diffuse necrosis with subsequent collapse of whole lobules, particularly in autopsy specimens. A submassive necrosis may leave parts of the parenchyma intact, which may undergo transformation into nodules. Then, features of cirrhosis, such as regenerative nodules and connective tissue septums linking portal tracts and central fields, become apparent, and, in a few cases, the diagnosis of active postnecrotic cirrhosis is justified. Because of the presence of relatively well-preserved parenchyma, it would appear that in these instances the fatal hepatic failure may have been caused by cholestasis reflected in bile infarcts rather than by the loss of liver cells.

The picture of the hepatitis as described above is dissimilar to that usually associated with the exposure to chemicals and which is reproducible in animals.[3] In such lesions, produced, for example, by carbon tetrachloride intoxication, one zone of the liver lobule is characteristically involved, and neighboring liver cells have a similar appearance. Such a picture is to be expected with a poison which has a metabolic effect and is uniformly distributed through the blood stream. Moreover, in toxic hepatitis, fatty metamorphosis is usually prominent, large cell breakdown products are abundant, and the inflammatory response, if present, is subdued and mainly characterized by segmented leukocytes.

In the cases under study, however, the diffuse distribution of the lesion and the conspicuous differences from cell to cell in the spotty necrotic stages would be more in keeping with an infectious process in which the causative agent grows at different rates in various cells. Such changes are typical, for instance, of the usual form of viral hepatitis. While viral hepatitis is not characterized by a single histological finding, a combination of several changes is taken as suggestive evidence for this disease.[4] Confirmation will be available when etiological tests have been developed.

The cases presented reveal all the pathological features of viral hepatitis listed in the classic description of both the nonfatal spotty necrotic form [4] and the fatal, usually massive necrotic form [5] of this disease. In this respect, the following findings in the material presented should be emphasized: the sparsity of breakdown products of hepatic cells in the necrosis; the early tendency of individual liver cells to regenerate; the mononuclear inflammatory

reaction with frequent admixture of eosinophils; and the conspicuous ductular proliferation and lipofuscin deposition, as well as the presence of acidophilic bodies in 17 cases and of phlebitis of the hepatic vein branches in 16 instances.

In keeping with these morphologic observations, the clinical picture is also that of a diffuse involvement of the hepatic parenchyma. Various gradations of the process are observed, including fatal hepatic insufficiency characterized by coma. Examples of recovery as well as of chronicity have been substantiated histologically. Viral hepatitis is known to produce a great variety of clinical pictures [8] which makes it difficult to decide on clinical grounds whether viral hepatitis is present in a patient with diffuse hepatic involvement. Several features in this series are not common in the usual type of viral hepatitis. First, fever was frequently absent. Second, jaundice was, on the average, deeper than usually seen. Third, the histological alterations in the biopsy specimens of the patients with jaundice after iproniazid administration were far more severe than in a random material of viral hepatitis, but this may be an incidental result of sampling. However, the histological alterations are also more severe than would be expected from the clinical manifestations. Particularly, the collapse of contiguous parts of the parenchyma is not often observed in biopsy specimens from patients with viral hepatitis. Many clinicians are hesitant to perform liver biopsy in the presence of such changes.

Finally, the high incidence of fatality, which often occurs with a fulminant course, indicates a much higher mortality than in the usual type of viral hepatitis, particularly in younger age groups. The numerical relation of autopsy to biopsy specimens in this material does not reflect the actual mortality, because autopsy specimens are more readily available than biopsy specimens. However, it is a safe assumption that the mortality is many times higher than that in viral hepatitis which, in the United States, is between 0.5 to 1%.[9]

The laboratory findings also support the concept of a diffuse disorder of the hepatic parenchyma in contrast to the hepatitis of the cholestatic type, such as may follow the administration of chlorpromazine.[1] However, in contrast to the situation in usual cases of viral hepatitis, cephalin flocculation is not quite as often abnormal and the thymol turbidity is less frequently very high. This has been considered characteristic of the serum type of hepatitis.[9] The frequent absence of febrile manifestations as well as the greater severity of the disease process, including a higher mortality and a more rapid course, have been observed [10] in some types of serum hepatitis, particularly when it occurs in elderly women.

The information on the dosage of iproniazid used in the cases presented was obtained mainly by means of a questionnaire. Taking these data at their face value, it is evident that the average total drug intake and the average daily dose were greater and that the average duration of drug therapy was longer in the fatal than in the nonfatal cases. However, the lack of statistical significance of these differences speaks against a definite relationship between the size of the daily dose and the duration of treatment with iproniazid on the one hand and the severity and outcome of the hepatitis on the other. A similar situation seems to exist with cinchophen, the administration of which is also associated with a very low incidence of hepatic necrosis of high mortality, without evidence of a relationship between dose and extent of lesion.[11]

In an attempt to clarify the possible etiological relation between iproniazid administration and the hepatic lesions observed, several possibilities must be considered. First, the hepatic disease may be not caused by iproniazid but is rather coincidental and may, for instance, be a viral infection transmitted by a poorly sterilized needle used in the course of other therapeutic procedures. This has been thought to be a possibility in the jaundice that occurs after administration of cinchophen.[11] However, it seems that the incidence of liver damage is much higher in these patients than in patients who were treated with other drugs and may have received parenteral therapy.

A second possibility is that iproniazid may produce a toxic effect which is indistinguishable from viral hepatitis. Acute yellow atrophy, resembling viral hepatitis, has been reported in a very low incidence after the administration of other drugs, e. g., sulfonamides [12] or zoxazolamine.[13] Thus, some drugs may produce occasionally the same metabolic changes as a virus, or both might elicit the same hyperergic reaction.

Before the inability to differentiate pathologically viral and toxic hepatitis is conceded, a third possibility should at least be considered, namely, that iproniazid activates subclinical viral hepatitis, particularly of the serum type (type SH or B). It is conceivable that this drug would produce an active disease process in a carrier. In view of the relatively low incidence of hepatitis in patients treated with iproniazid, it is apparent that not every carrier would develop jaundice if exposed to iproniazid. Further studies on the hepatitis associated with iproniazid therapy may throw new light on the mechanism of infection in viral hepatitis.

Because of the clinical and pathological similarity between the jaundice that occurs after administration of iproniazid and that which results from viral

hepatitis, it is readily understood why a causal relation between drug therapy and hepatic injury was not suspected until a considerable number of cases had occurred.

Whatever the mechanism, the fact that jaundice and diffuse hepatic injury, usually of great severity, occur in a small number of patients treated with iproniazid must be taken into account when prescribing this drug and invites, just as with other potent drugs, careful evaluation of the limitations, indications, and contraindications of iproniazid. Periodic checking by sensitive hepatic tests might reduce the risk.

Summary

A histological study was made of 13 biopsy specimens and 16 autopsy specimens of livers which were obtained in a nationwide collection from 27 patients who had developed jaundice after the administration of iproniazid (Marsilid) phosphate. The findings were correlated with the clinical manifestations of the hepatic disease and the dose of drug administered. The pathological picture was that of a diffuse hepatic parenchymal disease which ranged from a spotty necrosis of single cells to a diffuse massive necrosis and collapse, both associated with inflammatory infiltration. Tendency to transition into postnecrotic cirrhosis was apparent. The morphologic alterations were those considered characteristic of viral hepatitis. Histological evidence of preexisting liver disease was absent. Also, the clinical manifestations were those of a diffuse parenchymal involvement of the liver, but, in contrast to the usual cases of viral hepatitis, fever was frequently absent, the anatomic lesions were more severe than would be expected from the clinical picture, the jaundice was deeper, the process as a whole was more virulent, the mortality was higher, and the serum protein reactions were not as often altered.

A relationship between the dosage of iproniazid and the extent of the lesion was not evident, and jaundice appeared as late as 20 days after the cessation of therapy. The role which iproniazid may play in producing hepatic lesions is not clear; this is also true of other drugs such as cinchophen. The possibilities have to be considered that drugs such as iproniazid and others may produce morphologic changes previously considered characteristic of viral hepatitis in a low incidence or that these drugs may activate an existing subclinical vital hepatitis, e. g., in a carrier of serum hepatitis. Whatever the causal relation, the possible occurrence of severe hepatic damage with a deceptively less severe clinical picture but with a high mortality should be kept in mind when iproniazid is administered and should be weighed against its definite usefulness in patients with disabling depressions.

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Drs. Leo A. Pirk and Robert Dixon of the department of clinical investigation of Hoffmann-LaRoche, Inc., Nutley, N. J., made available for this study all pathological material collected by them as well as the pertinent information at their disposal. Clinicians and pathologists from many parts of the United States contributed findings and specimens.

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USES AND ABUSES OF THE TISSUE COMMITTEE

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A tissue committee is a group of physicians chosen within a hospital to review the histories of patients from whom tissues have been removed surgically; its purpose is to give an opinion on the correctness of the diagnosis and treatment. Data show that in the past there has been a marked diversity of practice among surgeons, with a lack of demonstrable abnormality in more than half of the appendixes removed by some surgeons. Since the formation of tissue committees, many improvements have been noted in the thoroughness of physical examinations, frequency of consultation, quality of operation, and preoperative and postoperative care. There has been a decrease in the frequency of subtotal hysterectomies, suspensoons of the uterus, ill-advised appendectomies, and other dubious, needless, or exploratory operations. The tissue committee is a device that has defects and dangers; but when made up of qualified, conscientious, and tactful physicians and properly organized with respect to the hospital, it has contributed greatly to the improvement of patient care.

Today most of the hospitals of the United States have some type of a committee, generally known as the tissue committee, set up for the control and evaluation of the surgery being done in a hospital. It is a requirement of the Joint Commission on the Accreditation of Hospitals. The problems in large teaching hospitals and in the smaller open staff hospitals are somewhat different. In this discussion we are referring mainly to the latter. We are working in two hospitals of this type: one has 150 beds and the other 125 beds. It is our purpose to try to point out some of the problems that confront such a committee in these hospitals because the committees are new and because they can do pioneer work if certain limitations are noted.

In the history of medicine, the control of itself for the benefit of others—the public—has always been paramount. In American medicine, the American Medical Association, the Association of Medical Colleges, and the American College of Surgeons, as well as other bodies, have been the forces behind our self-control programs. Today two other organizations, the Joint Commission on the Accreditation of Hospitals and the American Academy of General Practice have joined in this endeavor, not only in surgery but in all aspects of the practice of medicine. It is to be noted also that all of this work, all of this effort, has been exerted in order to control a small minority of doctors. A few individuals although properly trained and experienced are inclined to be unscrupulous. They require supervision and control on the part of conscientious colleagues.

In our particular hospitals the tissue committee is composed of the pathologist, the only continuing member, and three other members of the staff, who serve for a period of one year and are appointed by the chief of staff. Our open staff hospitals admit members of the county medical society to practice in the hospitals and therefore we have all types of physicians with all types of training and experience.

Our tissue committee functions in an advisory capacity only and has no executive powers. Decisions are based on the facts presented by the entire case in question. Neither a pathological ratio nor a strict auditing method is used as the sole criterion for decisions. It does not investigate all cases; for example, the orthopedic cases have not been investigated. It checks the cases where tissue has been submitted for examination. The research may show that, in the opinion of the tissue committee, certain diagnoses are not justified and why. It also brings up cases for open discussion at an executive meeting of the staff. Its findings are kept confidential, in that only members of the committee and the staff members are present at the discussions. Any doctor who has a case up for discussion is notified 24 hours in advance. The committee reports once a month to the staff meeting.

Since the formation of the tissue committees in our hospitals there have been many improvements noted in surgery, such as better records, better preoperative and postoperative care, more consultations, less doubtful and needless surgery, better examination of patients, and a fewer number of so-called exploratory operations. It is difficult for any doctor to exploit, during surgical exploration, the female pelvis, the gall-bladder, or the appendix or to do any questionable surgery without its being known by the tissue committee, who would call his attention to it. It is also noted that most of the

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doctors try to limit themselves to those surgical procedures that are more consistent with their training and experience.

The following suggestions brought out by the tissue committee have been adopted by our hospitals: (1) a uniform code for the sterilization of

TABLE 1.—*Percentage of Pathological Findings in Appendectomies in One Hospital*

No. Removed	% Pathological	No. Removed	% Pathological
89	54	19	74
51	49	18	66
46	85	18	55
47	87	15	73
38	54	13	70
28	70	9	77
27	66	8	63
23	69	5	80
22	86	5	80
20	85		

patients in one of our hospitals, (2) the routine performance of proctoscopic or sigmoidoscopic examination prior to hemorrhoid operations, (3) the routine pathological examination of all tissues removed at operation except tonsils, and (4) the routine performance of total hysterectomy rather than subtotal hysterectomy except in rare instances. The improvements brought out by the activity of the tissue committee have stimulated the staff at one hospital to appoint a medical audit committee and to hold a monthly death conference.

Defects of Committee

On the other hand, it is recognized that abuses can occur in the functioning of a tissue committee. Medicolegal hazards may possibly develop, and malpractice suits could be generated by the actions of the committee. It is our feeling that the record of its activities should not be preserved except in tabular form, thereby preventing the identification of the action of the tissue committee in any given case, and that use of specific names of staff members be avoided. This practice of not keeping identifiable records may not fully meet the requirements of the Joint Commission, but we hope they will recognize this legal implication and act accordingly. Physicians should be advised to be discreet and not to discuss the specific activities of the tissue committee among themselves in the presence of curious hospital personnel, since this might lead to misunderstanding and malicious gossip.

Another point to recognize is that the activities of the tissue committee may make a too conscientious doctor fail to use his better judgment at times. It may lead to undue procrastination, as in cases of surgical abdomens. Some doctors will not accept criticism and insist on their individual rights to practice medicine as they see fit. Some defy the tissue committee and others try too hard to please. Some abuse it by defending other doctors when they definitely need criticism. In small hospitals with few doctors on the staff, the doctors are very close to each other and do not like to criticize the work of others. In such instances, it is suggested that doctors from other hospitals be asked to serve on the tissue committee.

Some small hospitals do not have pathologists on their staffs. A pathologist is not indispensable, although his findings usually are a definite aid. Most physicians accept the findings of the tissue committee with dignity. Many have been heard to say that they learn more from these reports and discussions than from any other one meeting that they attend.

Statistical Data

The following statistical data demonstrate some of the problems and results encountered in our program. From 1953 to 1957, a total of 219 gallbladders were removed in one of our hospitals. Of these, 185 (85%) were pathological. Improvement is needed here, but without the work of the tissue committee we would not have known it. In another hospital 95 gallbladders were removed in the same period. Of these, 92% were found to be pathological.

The appendectomies done in a hospital always seem to reflect in some manner the surgery being done. In 1956 in one hospital 107 appendectomies were performed; 70 (66%) were pathological. In another hospital 111 appendectomies were done; 72 (65%) were pathological. In a third hospital 153 appendectomies were performed; 126 (82%) were pathological. Table 1 gives records kept in one hospital for physicians who did five or more appendectomies from 1954 to 1957. The appendix was judged pathological if any type disease was found by the pathologist.

In the field of pelvic surgery, in one hospital 41 suspensions were performed in 1951, 25 in 1952, 30 in 1953, 14 in 1954, and 10 in 1955. At another hospital 36 suspensions were performed in 1950 and only 4 in 1956. The following table shows the decline in subtotal hysterectomies performed.

Since the records in our hospitals prior to the formation of the tissue committees are not adequate, many true relationships cannot be shown.

TABLE 2.—*Hysterectomies Performed in Three Hospitals*

	Hospitals					
	1		2		3	
	1951	1955	1951	1955	1950	1956
Total	142	132	53	61	111	250
Subtotal	73	11	25	16	71	12

Also, one of the hospitals is new and no prior records are available. Even so, improvement from a surgical standpoint can be seen.

Comment

It is our firm belief that the following recommendations, if adopted, would further aid in developing and maintaining high standards of surgery being done in our smaller open staff hospitals: 1.

Give the tissue committee executive power. 2. The tissue committee should be composed of doctors who have proper training and/or experience, and who are willing to actively work on the committee in an absolutely unbiased manner. 3. Full surgical privileges should not be granted to inadequately trained and inadequately experienced physicians; every staff member should be granted privileges according to his demonstrated competence regardless of the certificates he may hold. 4. Similar committees should be formed in other departments, such as medicine and obstetrics. 5. Local control of the practice of medicine and surgery is far better than control from Washington, Chicago, or elsewhere. 6. If no pathologist is available, the tissue committee should function just as effectively. 7. If the staff is too small to have an effective committee, neighboring doctors should be asked to serve on such a committee. It is obvious that the work of the tissue committee in hospitals has improved the quality of patient care.

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EFFECT OF AIR FLOW RESISTANCE ON VENTILATION AND RESPIRATORY MUSCLE ACTIVITY

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As measured in decerebrate cats, inspiratory air flow resistance initially reduces the tidal volume and frequency of respiration. The reduction in tidal volume is aggravated by pentobarbital, nitrous oxide, or ether. If the flow resistance persists, there is a gradual recovery in the volume of ventilation, but even in the unanesthetized state this is not complete at the end of five minutes. Ventilation is reduced with increased airway resistance in spite of augmented muscular activity. The reduction of ventilation is proportional to the magnitude of the resistance.

Although there is general agreement that increased resistance to air flow has an adverse effect on ventilation, there have been very few quantitative studies of this subject. Recently it was reported [1] that in man an added airway resistance maintained for five minutes caused a reduction in pulmonary ventilation and a rise in alveolar carbon dioxide tension. The object of the present study was to measure the effect of air flow resistance on ventilation and diaphragmatic muscular activity. The influence of anesthetic agents on the response to increased airway resistance was also investigated.

Method

Studies were made on decerebrate cats in order to obtain continuous observation of the unanesthetized and anesthetized states. Decerebration was performed at midcollicular level during diethyl ether anesthesia. Measurements were made one hour or more after the completion of decerebration, at which time the preparation was stable and most of the ether eliminated. Control observations were made while the animals breathed room air. Nitrous oxide–oxygen or diethyl ether oxygen mixture was introduced through a non-rebreathing valve. Pentobarbital sodium in divided doses was administered intravenously.

Recordings were made with the use of five channels of an eight-channel cathode-ray oscillograph. The tidal volume was measured with a small animal pneumotachograph and displayed on one channel of the recorder, the output of which was integrated electronically, with use of a second channel. The airway pressure was obtained with a strain-gauge transducer. The action potentials of the diaphragm from two monopolar electrodes inserted through the ninth intercostal space were amplified and recorded on the fourth channel. In addition, the electromyogram was integrated on the fifth channel, thus providing an estimate of total electrical activity as well as the frequency of dis-

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charge. It is known that under specific conditions the integral of the electromyogram is proportional to the tension developed by the muscle.[3] In the case of the diaphragm the present study suggests that the slope of the integral during inspiration indicates the intensity of the muscular activity required for the observed flow of air.

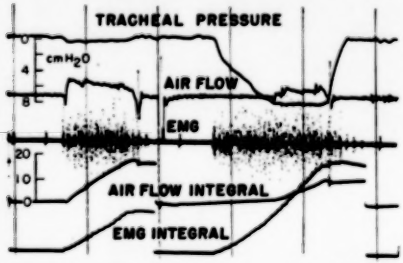

Fig. 1 (cat 27).—Actual record of normal respiration followed by one inspiration against added load of −8 cm. H_2O in unanesthetized cat. Tidal volume is measured by vertical displacement of air flow integral. Electromyogram *(EMG)* shows prolongation of diaphragmatic contraction with application of resistance, and intensity, shown by slope of electromyogram integral, increases until air flow begins, thereafter remaining steady (time lines=one second).

Inspiratory resistance to air flow was introduced by means of a vacuum-cleaner fan connected to the non-rebreathing valve through a three-way tap. The third limb of the tap led to room air or to the anesthetic reservoir. The speed of the fan was regulated by a variable transformer; the magnitude of the negative pressure generated was monitored with a water manometer. The negative pressure, when applied for single breaths by turning the three-way tap, constituted an accurately controlled inspiratory resistance. For the study of continuous inspiratory resistance during inhalation anesthesia, the resistance consisted of an appropriately weighted inspiratory valve. This allowed continued inhalation of the anesthetic mixture so that the depth of anesthesia would not be changed appreciably during the test period.

Eighteen animals were studied and were divided into four groups. In groups 1, 2, and 3, graduated resistances in steps of 2 cm. H_2O were applied for single breaths at one-minute intervals, before and after administration of anesthetics, as follows: group 1 (five cats), pentobarbital sodium given intravenously in successive doses of 6 mg. per kilogram of body weight; group 2 (four cats), 80% concentration of nitrous oxide and 20% concentration of oxygen; and group 3 (four cats), three increasing concentrations of diethyl ether vapor in oxygen. Inhalation of these anesthetic mixtures was maintained for 30 minutes before any measurement was taken so that a relatively steady state was obtained. The ether mixtures were obtained by appropriate dilution of the outflow from a "copper kettle" at the observed temperature. The ether concentration was estimated indirectly with a Pauling oxygen analyzer. In group 4 (five cats), continuous resistance to inspiration was applied for five minutes before and during anesthesia with pentobarbital or ether. Respiratory frequency, tidal volume, and diaphragmatic muscular activity were measured continuously.

Results

Unanesthetized State.—A typical example of the immediate response to increased inspiratory resistance is reproduced in figure 1. This is a record of two successive respirations: first, the control and, second, inspiration against an added resistance of −8 cm. H_2O. In the control breath, the duration of air flow corresponded almost exactly with the period of electrical discharge of the diaphragm and both integrals rose at a steady rate, indicating that the rate of air flow and the intensity of diaphragmatic contraction remained constant throughout most of the inspiratory phase. In the second breath, the air flow volume was diminished and the air flow rate was reduced, as indicated by the height and slope of the integral. The onset of inspiratory air flow was much delayed in respect to the muscular activity. The diaphragmatic contraction was prolonged and increased in intensity, as evidenced by the steeper slope of the electromyographic integral. When the response to a series of increasing air flow resistances was examined, the reduction in tidal volume was proportional to the added resistance, notwithstanding a concomitant proportionate increase in diaphragmatic activity (fig. 2). The fact that the increased diaphragmatic activity occurred immediately on application of the resist-

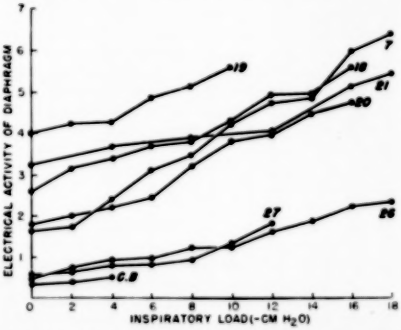

Fig. 2.—Effect of inspiratory resistance on diaphragmatic activity. Voltage output of muscle increases approximately linearly with load; increased activity was not sufficient to maintain normal tidal volume.

ance suggests that this is a reflex phenomenon, probably through the Hering-Breuer stretch reflex, since it was abolished by bilateral vagotomy.

When the resistance was maintained continuously for five minutes, the diaphragmatic activity increased in successive breaths over the first half-minute. The tidal volume decreased initially on application of resistance and recovered gradually during the five-minute period but never to the original level.

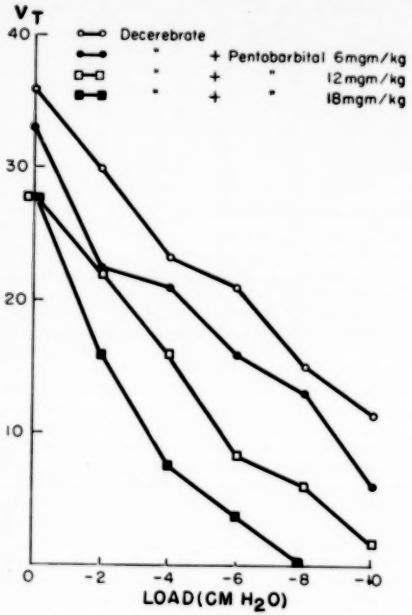

Fig. 3.—Effect of pentobarbital sodium on ventilation during inspiratory flow resistance. Ability to overcome flow resistance decreased as more drug was administered.

Anesthetized State.—The effect of pentobarbital sodium on the immediate response to inspiratory resistance was as follows: The volume and rate of air flow against the added resistance were reduced to a greater extent as compared with those in the unanesthetized animal. The diaphragmatic contraction was prolonged but showed little increase in intensity.

Application of a series of increasing inspiratory resistances caused a reduction in tidal volume proportional to the magnitude of the resistance (fig. 3), the decline occurring more rapidly with each additional dose of pentobarbital. Thus, the fractional decrease in tidal volume produced by a given resistance was relatively greater as the anesthesia was deeper. In this respect, the effects of nitrous oxide and diethyl ether were without exception similar to those of pentobarbital, as shown in figure 4. Evidently, general anesthesia exaggerates the impairment of ventilation caused by inspiratory air flow resistance, and this impairment becomes progressively more pronounced as anesthesia deepens.

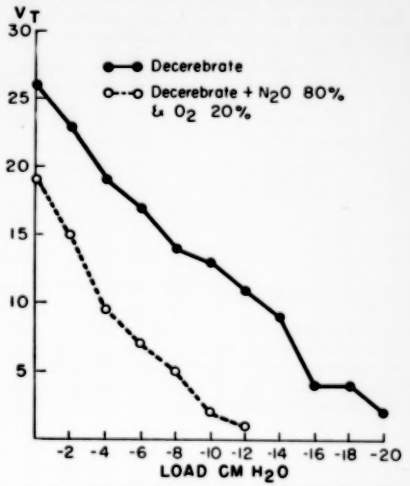

Fig. 4.—Effect of nitrous oxide on ventilation during inspiratory flow resistance, showing depression of tidal volume by anesthesia.

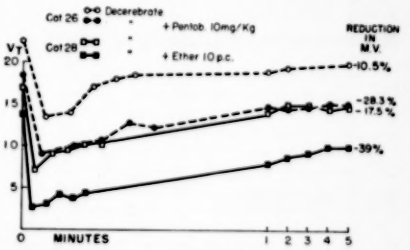

Fig. 5.—Inspiratory resistance of −12 cm. H_2O sustained for five minutes. During pentobarbital and diethyl ether anesthesia, depression of tidal volume by resistance was increased and recovery of minute volume delayed.

The effect of pentobarbital and diethyl ether anesthesia on the adjustment to sustained inspiratory resistance is shown in figure 5. The reduction

in minute volume was much greater after the animals were anesthetized (see table). The higher respiratory rate with ether anesthesia apparently did not compensate for decreased tidal volume.

Comment

Relatively high resistances (6-15 cm. H_2O) were used in the sustained resistance experiments in order to produce significant disturbances in a short period of time. Similar but less marked responses were produced with lower resistances, even with the low resistances of clinical anesthesia apparatus. Figure 6 shows the effect on respiratory muscle activity of connecting a Heidbrink circle machine to the endotracheal tube of a patient anesthetized with nitrous oxide–oxygen and thiopental. Expiratory activity was increased, as shown by the rise of the electromyographic integral, and there was also a slight prolongation of inspiratory activity.

Effect on Ventilation of Inspiratory Resistance Maintained for Five Minutes

Cat, No.	Resistance, Load, Cm. H_2O	Anesthesia	Tidal Volume* Before Loading	Tidal Volume* After Loading	Respirations per Minute Before Loading	Respirations per Minute After Loading	Minute Volume* Before Loading	Minute Volume* After Loading	Change, %
25	−6	None	22	22	20.7	18.7	454	414	−8.8
		Pentobarbital, 10 mg./kg. of body weight	21	19.3	16	13.8	336	266	−21.7
26	−12	None	25	20	10.5	12	268	240	−10.5
27	−12	None	18.5	15	12.4	9.8	240	147	−28.8
		Pentobarbital, 10 mg./kg. of body weight	18	16.5	29.6	29.5	535	486	−10.5
		Pentobarbital, 10 mg./kg. of body weight	18	14	29.5	25.6	530	358	−32.5
28	−12	None	17	15	19.4	18	328	270	−17.5
		Ether, 10%	13.7	10	22.7	21.4	351	214	−39.0
29	−15	None	23	24	15	17	345	408	+18.0
		Ether, 5%	36	26	13.6	11.7	495	305	−38.5

* In arbitrary units of 1.5 ml.

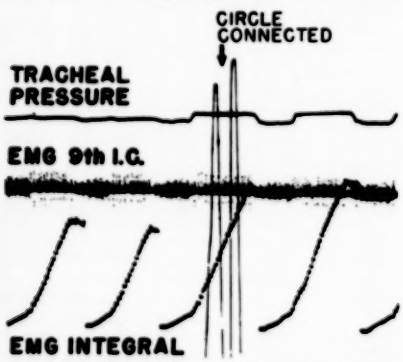

Fig. 6.—Ninth intercostal muscle activity during nitrous oxide–oxygen and thiopental anesthesia in man. At signal, circle machine was reconnected to endotracheal tube, resulting in increased fluctuations in intratracheal pressure (*upper trace*), as well as prolongation of expiratory activity, shown by greater rise of electromyographic (*EMG*) integral (*bottom trace*). There is also slight prolongation of inspiratory discharge.

Nitrous oxide is usually believed not to depress respiration,[3] although Seevers and Waters [4] have pointed out the dearth of quantitative observations concerning this gas and much of the early work on nitrous oxide anesthesia is vitiated by concomitant hypoxia. In our experiments, all the cats anesthetized with 80% nitrous oxide–oxygen (group 2) showed a diminished ability to inspire against an added resistance applied for a single breath. Arterial oxygen tensions were not measured, but, under the conditions of the experiment, any hypoxia would have been due to depression of ventilation by the anesthetic, since obstruction lasted for only one breath in each minute. The result would support the conclusion that nitrous oxide does, in fact, depress respiratory activity (fig. 4).

The stimulatory effect of light ether anesthesia on ventilation was observed in all the cats in group 3, chiefly as increased frequency of respiration, but, in spite of this stimulation, the animals' ability to overcome an inspiratory resistance was impaired (fig. 5) and the impairment became greater with each increase in the anesthetic vapor concentration.

From these experiments it appears that inspiratory resistance initially reduces the tidal volume and frequency of respiration and that the reduction in tidal volume is aggravated by pentobarbital, nitrous oxide, or ether anesthetic. If the flow resistance persists, there is a gradual recovery in the volume of ventilation, but even in the unanesthetized state this is not complete at the end of five minutes. This agrees with the findings of Zechman and co-workers [1] in man. Furthermore, the recovery rate is much slower during pentobarbital or ether anesthesia, indicating that the animal's compensatory mechanism was also disrupted to a certain extent.

Summary

The effect of added airway resistance on ventilation and respiratory muscular activity was studied in decerebrate cats before and during anesthesia. The ventilation was reduced with increased airway resistance in spite of augmented muscular activity.

The reduction of ventilation was proportional to the magnitude of the resistance. General anesthesia with pentobarbital, nitrous oxide, and ether aggravated this ventilatory disturbance; the impairment became progressively greater with deeper anesthesia.

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MANUAL AND MECHANICAL CONTROL OF VENTILATION DURING CYCLOPROPANE ANESTHESIA

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Respiratory factors that might be responsible for the appearance of cardiac arrhythmias during cyclopropane anesthesia were studied in 34 patients. Respiration was controlled manually in 15 cases and mechanically in 14; in 5 the control was manual in the beginning and mechanical later on. In the presence of such control, high blood levels of cyclopropane were quite compatible with adequate oxygenation as gauged by determinations of oxygen saturation, carbon dioxide tension, and pH. Electrocardiographic changes, interpreted as a shifting of the pacemaker toward the atrioventricular node, occurred repeatedly in five cases but were not associated with any noticeable cardiac irregularity. Distinctly palpable arrhythmias occurred in two patients; in one of these spontaneous respiration had been permitted early in the anesthesia and in the other there were indications of underlying cardiovascular instability. Under the conditions of this study hyperventilation was more frequent than hypoventilation. The evidence showed that cardiac arrhythmias perceptible by palpation should rarely occur when cyclopropane is administered with ventilatory control.

This study was undertaken originally to determine whether cardiac arrhythmias would occur consistently with cyclopropane anesthesia when respiration of the patient was controlled by the anesthetist. The respiratory depression usually caused by cyclopropane could be avoided by controlled ventilation. A comparison of manual and mechanical control of ventilation during anesthesia arose as an outgrowth of this study. Cyclopropane levels, oxygen content and capacity, carbon dioxide content and tension, and pH were determined in arterial blood prior to induction of anesthesia and at varying intervals during the course of surgery.

Materials and Methods

Thirty-four patients, ranging in age from 28 to 77 years, were selected at random for this study. With one exception, all underwent major intra-abdominal surgery. All but one were free from pulmonary symptoms and disease. Respiration was controlled manually in 15 cases and mechanically by a Jefferson ventilator in 14 cases; in five patients respiration was managed first by manual control and later by ventilator control. The electrocardiogram was monitored in 16 cases, and permanent tracings were made if any change in rate or pattern occurred. Control samples of arterial blood were drawn after

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the patients had been breathing oxygen at a high flow (8-10 liters per minute) on a semiclosed system for 15 to 30 minutes. Anesthesia was induced by injection of a small amount of thiopental sodium, and endotracheal intubation was facilitated by ad-

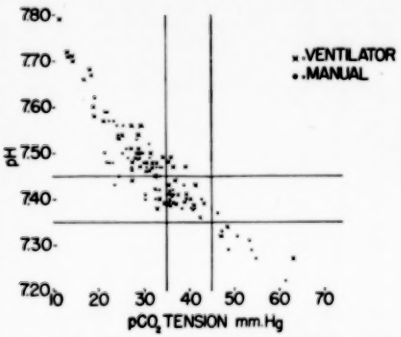

Fig. 1.—Incidence of hyperventilation and alkalosis with use of manually and mechanically controlled respiration during cyclopropane anesthesia.

ministration of succinylcholine chloride. Cyclopropane anesthesia was begun immediately after intubation. When the Jefferson ventilator was being used, aliquots of gas from the inhalation stream were drawn at the time of arterial sampling and analyzed in a Scholander apparatus for percentage of oxygen in the inspired gas. This was compared with the percentage of oxygen flowing from the gas machine.

Carbon dioxide and oxygen contents of arterial blood were determined on whole blood by the Van Slyke-Neill method,[1] modified for the presence of cyclopropane.[2] Cyclopropane level was determined by a method described previously.[3]

Results

In the majority of cases, there was a certain degree of hyperventilation with resultant alkalosis (fig. 1). This was more marked in the ventilator-controlled group. The carbon dioxide content of arterial blood decreased in each group but much more in the ventilator group. The mean carbon dioxide tension of plasma remained relatively steady in the manual and manual-ventilator groups but showed a pronounced drop in the ventilator group. Marked alkalosis (pH more than 7.55) was present in three cases when respiration was controlled manually and in five cases when ventilator control was used. Seven patients passed through periods of acidosis, but only two patients showed respiratory acidosis at the time of the last sampling. A graphic comparison of the findings in the manually controlled and the ventilator-controlled groups is shown in figure 2.

The control specimens of arterial blood were drawn after the patients had breathed 100% oxygen for 15 to 30 minutes. Despite this, the hemoglobin saturation with oxygen was frequently less than 100%. (Oxygen contents were corrected for oxygen dissolved in the plasma according to Comroe.[4]) The average control value was 97.3% saturation. Suboxygenation of control samples of arterial blood was apparently not the result of over-all hypoventilation, since plasma carbon dioxide tension was always within the normal range. It was more likely related to uneven alveolar ventilation and perfusion as the result of postural inactivity after premedication (fig. 3).

During cyclopropane anesthesia, the oxygen saturation tended to approach an average of 92% regardless of the type of ventilatory control. High blood levels of cyclopropane were not necessarily associated with poor oxygenation. In the latter part of our study, we determined the percentage of oxygen in the cyclopropane-oxygen mixture being

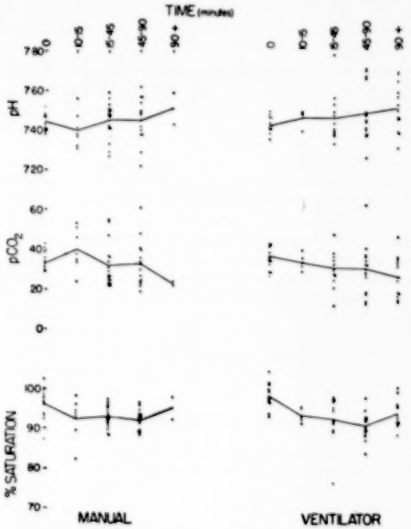

Fig. 2.—Comparison of findings in manually controlled and ventilator-controlled groups during cyclopropane anesthesia.

delivered to the patient by the Scholander analysis.[5] As was expected, the oxygen concentration of the inspired gas was always less (average, 62.8%) than that calculated from the flow meter (average, 79.4%), since the inspired gas was diluted by recirculated gas from the rebreathing bag. When the Scholander analyses were carried out, the value

for inspired oxygen concentration so obtained was used in correcting arterial oxygen content for dissolved oxygen in the plasma.

In 16 cases, the electrocardiogram was monitored and permanent tracings made at the time of arterial blood sampling. It was our original purpose to correlate the incidence of cardiac arrhythmias occurring during cyclopropane anesthesia with arterial blood levels of cyclopropane, oxygen, carbon dioxide tension, and pH. Assuming that arrhythmias might occur during deep anesthesia, we attempted to push anesthetic levels as deep as possible while monitoring the electrocardiogram for changes in rhythm. Respiration was controlled manually in eight cases and by the Jefferson ventilator in eight cases.

when it did occur lightening the anesthesia seemed to shift the pacemaker upward. There was a tendency for the arterial oxygen saturation to be moderately decreased at the time of the displaced pacemaker (89-92% saturation). Correlation with the clinical records of these five patients suggested that preexisting heart disease, momentary hypoxia or hypotension, or prior treatment with quinidine, digitalis, or thyroid extract contributed to the development of a wandering pacemaker during cyclopropane anesthesia.

In two cases distinctly palpable, potentially dangerous arrhythmias occurred. Frequent premature ventricular beats and bigeminy were noted on the electrocardiogram. One of these was the only case in which respiration was allowed to be spontane-

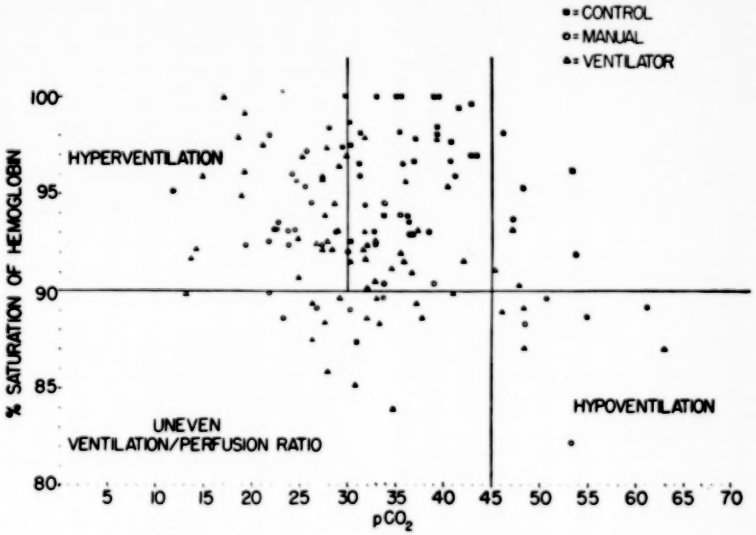

Fig. 3.—Ventilation and perfusion during cyclopropane anesthesia.

We found it impossible to provoke cardiac arrhythmias at will under these conditions when cyclopropane was administered by controlled ventilation. Deep anesthesia (cyclopropane level more than 15 mg. %) did not cause cardiac irregularities or consistent electrocardiographic changes, nor was light anesthesia a provocative agent.

The most common electrocardiographic alteration was an occasional shift of the cardiac pacemaker downward toward the atrioventricular node. This was unassociated with any noticeable cardiac irregularity and occurred repeatedly in five cases. It was unrelated to depth of anesthesia, although

ous early in the anesthetic course, and respiratory acidosis (pH 7.29) together with moderately deep cyclopropane anesthesia existed at the time of the arrhythmia. Institution of manually controlled ventilation with return of the pH to 7.45 and slightly lighter anesthesia returned the electrocardiogram to normal. In the other case there was an unusually labile, elevated blood pressure. Arterial oxygenation was excellent throughout, and a constant respiratory alkalosis existed. The labile blood pressure and cardiac irregularity could not be explained. It might be assumed that delivery of oxygen to the myocardium was less than perfect.

Comment

Cyclopropane is a potent respiratory depressant, and its administration after that of preanesthetic drugs may result in hypoventilation, notably causing carbon dioxide retention, respiratory acidosis, and, occasionally, suboxygenation despite a high oxygen mixture. Control of respiration can be readily established either manually or mechanically, and respiratory acidosis can be avoided. Vigorous control of respiration will produce respiratory alkalosis by washing out carbon dioxide. We found overventilation to be more common than underventilation when artificial respiration was used.

The low carbon dioxide tension of respiratory alkalosis favors a more tenacious binding of oxygen and hemoglobin, whereas a high carbon dioxide tension favors dissociation of oxyhemoglobin.[6] We have not found clinical evidence that hyperventilation with respiratory alkalosis to the degree seen in these cases is harmful to the anesthetized patient. This corroborates the findings of other investigators.[7] The circulatory status of these patients was stable in most instances, and variations which did occur were apparently unrelated to respiratory control. Since carbon dioxide is a potent vasodilator, it has been suggested that coronary vasoconstriction may follow its decrease in the blood by hyperventilation.[8] In the present study, respiratory alkalosis was not associated with consistent electrocardiographic changes. If alkalosis was sufficient to produce coronary vasoconstriction, it was not so severe as to produce myocardial ischemia in the presence of the oxygen concentrations employed. Recovery from anesthesia was prompt in all cases, and there was no clinical evidence of cerebral impairment as a result of altered acid-base balance and cerebral circulation.

Despite hyperventilation sufficient to produce respiratory alkalosis, arterial blood oxygenation may be unexpectedly low because of uneven ventilation and perfusion of the lungs. In this study, when the inspired gas mixture contained 80% or more oxygen by the Scholander analysis, the uncorrected oxygen content of arterial blood was invariably greater than the oxygen capacity, indicating considerable oxygen dissolved in plasma. When the inspired oxygen concentration was 55% or less, the uncorrected oxygen content was less than the oxygen capacity, indicating hemoglobin unsaturation. Nahas and co-workers[9] showed that hemoglobin saturation was significantly less than 100% when healthy male subjects breathed 40, 50, and 60% oxygen. Our figures roughly corroborate these findings. Inspired gas oxygen concentration of 70% or more should yield arterial oxygen tensions of more than 400 mm. Hg; at this level uncorrected arterial oxygen content was usually higher than oxygen capacity.

Direct oxygen tension measurements in the presence of gaseous anesthetic agents are difficult and, as yet, not perfected. The most reliable means yet devised for determining relative difference in oxygen saturation at oxygen tensions more than 100 mm. Hg is by oximetry. The oxygen saturations calculated from the tonometric determinations of oxygen capacity give results which are about 2% below the values of oxygen saturation as determined by oximetry.[9]

Summary

Controlled ventilation during cyclopropane anesthesia by either manual or mechanical means usually produces hyperventilation and respiratory alkalosis. Oxygenation of arterial blood may be less than 100% even in the presence of hyperventilation if there is uneven ventilation and perfusion of the lungs. Cardiac arrhythmias perceptible by palpation rarely occur when cyclopropane is administered with ventilatory control. Downward displacement of the cardiac pacemaker as seen on the electrocardiogram may represent myocardial depression by cyclopropane superimposed on preexisting myocardial disease or drug therapy.

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Dorothy W. Ellis provided technical assistance and Dr. William L. Winters reviewed electrocardiographic records for this study.

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FACTORS TO BE CONSIDERED IN PLANNING A REHABILITATION SERVICE

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With the accumulation of new knowledge regarding techniques for the rehabilitation of patients with handicaps, many communities both in the United States and elsewhere are developing or planning to develop new "rehabilitation services." As with any relatively new field, there is agreement concerning some aspects of rehabilitation services and lively discussion about other aspects. Because in most communities there is a limitation of both funds and trained personnel, sound planning is essential in order that the available funds and personnel may serve the greatest number of patients most effectively. It is the intent of this paper to describe briefly some of the factors and principles to be considered in planning a rehabilitation service, as a guide for persons or for a community contemplating the development of such a service.

A rehabilitation service might reasonably be expected to carry out at least three functions: patient care, research, and training of professional personnel of all types. The advantages of location in a general hospital include the ready availability of all types of medical specialists and consultants; provision of both inpatient and outpatient care; avoidance of duplication of certain types of facilities; the possibility of earlier referral of patients; better dissemination of knowledge concerning rehabilitation; the possibility of the wider use of rehabilitation principles in the care of other patients within the general hospital; and the provision of surgical services in the same hospital in which the rehabilitation service is located. Unless a plan is made and carried through for the patient's continuing care and supervision, frequently he may receive little or no aftercare and may regress. Until more knowledge is available regarding primary prevention of many chronic diseases in both children and adults, rehabilitation services will be needed.

Functions and Location of a Rehabilitation Service

Functions.—A rehabilitation service might reasonably be expected to carry out at least three functions: 1. Patient care. This includes such phases as evaluation, diagnosis, treatment, vocational restoration, and continuing long-term care and supervision, on both an inpatient and outpatient basis. This primary function should include the evaluation of the results of the rehabilitation both of individual patients and of groups of patients. 2. Research. Especially to be noted is the area of experimentation with new methods and techniques of rehabilitation and of the evaluation of such experimentation. 3. Training of professional personnel of all types. This includes medical personnel (especially physiatrists, pediatricians, and internists), nurses (both hospital and public health), physical, occupational, and speech therapists, psychologists, vocational counselors, social workers, recreation workers, and others.

Location.—One of the controversial issues is that of location of the rehabilitation service. Possible locations include the development of (1) a rehabilitation service in a general hospital, (2) a rehabilitation service in a specialty hospital, such as that for orthopedic surgery, chronic disease, or otolaryngology, and (3) a completely separate rehabilitation "center." While we are in favor of the location of the rehabilitation service within the general hospital, we recognize that local circumstances may favor its development in another location.

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The advantages of location in a general hospital include the ready availability of all types of medical specialists and consultants; provision of both inpatient and outpatient care; avoidance of duplication of certain types of facilities, such as laboratory or x-ray services; the possibility of earlier referral of patients in the general hospital for rehabilitation, because the rehabilitation service is an integral part of the general hospital; better dissemination of knowledge concerning rehabilitation to other members of the general hospital staff, both medical and nonmedical; the possibility of the wider use of rehabilitation principles in the care of other patients within the general hospital; the specific assignment of individual physicians from other services of the hospital, so that responsibility is fixed and so that there may be cross-fertilization of ideas regarding patient care; and the provision of surgical services in the same hospital in which the rehabilitation service is located, so that there may be some continuity of care prior to and immediately after the surgical phase.

In the event that location within a general hospital is not possible, steps should be taken to assure the same quality of medical and health care as would be provided there. These steps include medical direction by a qualified physiatrist, preferably on a full-time basis; the provision, assignment, and easy availability of other medical specialists; a close working relationship with all other hospitals of the community, so that patients will be referred early to the rehabilitation service; when surgery is indicated, the working out of a careful plan with the surgical staff regarding timing, responsibility for joint supervision of the patient, continuity of care, and other factors; and provision of both inpatient and outpatient care and a unity system of records, so that continuity of care will be fostered. Also, a preferable location would be in a facility used for teaching purposes for the undergraduate and postgraduate training of professional personnel.

At the state level, thought should be given not only to planning for the rehabilitation service's location within the state capital or the central city but also to providing for regional or district rehabilitation services to meet the diagnostic, treatment, follow-up, and supervision needs on a long-term basis. This means, then, planning the services geographically so that they will be easily available to all citizens of the state on a regional or district basis.

A completely planned rehabilitation program must include local medical, nursing, social, and vocational counseling services to assist the handicapped patient in his return to normal community living. After the initial readjustment, some handicapped persons require little additional help. Others may need assistance and counseling for a long time before they achieve independence. The rehabilitation team in the local community can initiate the rehabilitation program for a handicapped patient early in the course of the disease, handle the entire rehabilitation program of the patient with less involvement, and be available to supervise and assist when the patient returns home again.

At the local level, other factors may warrant consideration in deciding on location. For example, the presence of a school for handicapped children, of a housing project with a fair number of handicapped people, or of a sheltered workshop may make it desirable to locate the rehabilitation service nearby for the convenience of these patients in order to reduce transportation costs and facilitate continuity of care.

Types of Patients

One of the basic decisions to be made is that regarding the types of patients to be cared for in the rehabilitation service. Is the service to be used for one or a few diagnostic types of patients, or is it to be used for all types of handicapped patients? On this basic decision will depend such essential aspects as the plan for the physical plant and staff. Both patterns have been used in the United States, and it is our opinion that, where a service is developed for patients with a variety of conditions, it is more likely to be of higher caliber, it can have a more complete staff, it is possible that the cost per patient will be lower because a reasonably complete staff can be provided, and more patients in the community are likely to be served. However, these are empirical observations, and objective studies of both methods are necessary.

Where a service is developed for one or a few diagnostic groups only, those patients included are likely to receive more concentrated care in a limited way. For example, the development of special separate services for patients with cerebral palsy has undoubtedly resulted in better care than previously existed; however, the provision of such separate services has usually meant that an ophthalmologist is rarely provided as a staff member of the cerebral palsy program. It has also meant that the hearing aspects of diagnostic and therapeutic care are frequently forgotten, overlooked, or, when provided, inadequate in quality. It is thought that the provision of a rehabilitation service for a larger number of diagnostic groups of patients will mean that all essential aspects of patient care will be considered for all patients.

In this connection, the question frequently is raised regarding the advisability of providing separate rehabilitation services for children and adults. Reasons advanced for the separation of children's services include the facts that children's needs are different and that the children's service may be of inferior quality because it may be overshadowed by the adult service. In our opinion, separation is unnecessary and may be undesirable because of the possibility of duplication of services and wastage of available funds and personnel. We believe that, if some program modifications can be made, it is more desirable to have the children's and adults' services together. These modifications include the need for staff understanding of the physical and emotional growth and development of children, the inclusion of a pediatrician on the staff, the provision of equipment of a size appropriate for children, consideration of children's educational and vocational needs, and the employment of a clinical psychologist who has had training and experience in working with children.

The Staff

There is general agreement that a multidisciplined staff is essential for a rehabilitation service. The composition of the staff to a certain extent is determined by the type of patients to be cared for. In a service caring for a wide variety of types of patients, personnel considered essential are as follows: the medical staff (especially the physiatrist, pediatrician for children, internist for adults, psychiatrist, ophthalmologist, orthopedic surgeon, cardiologist, surgeon, otologist, neurologist, and urologist); the nursing staff (staffs of both the institution and the community public health nursing

agency); social service; dental and orthodontic service; therapists (physical, occupational, and speech); the psychologist; the vocational counselor; the audiologist; the recreation worker; technician services (laboratory, x-ray, electroencephalographic, and orthoptic); and the teacher.

It is evident that the list is long and that the cost of a reasonably complete service is high. The many facets of patient care—medical, social, psychological, educational, vocational, and recreational—must be considered together if the patient is to be assisted as a whole person. This means that the staff members must be provided with an opportunity and must be able to work together as a team or unit. If the team effort is not used, it may mean that the patient may be shunted from one staff member to another, timing of services may be incorrect, some available services may actually not be used for a patient, and the total essential needs of the patient and his family may not be considered.

One other aspect of the subject of the staff of the rehabilitation service merits discussion: direction of the service. There is general agreement that a full-time director is essential. Two patterns of directorship of rehabilitation services have developed in the United States: (1) the physician as full-time director and (2) a nonmedical staff member as full-time director, with the physician as full-time or part-time medical consultant. It is our opinion that the full-time director should be a physician—one who is interested and trained in the field of rehabilitation. Reasons for the need of a full-time medical director include the fact that there are primary medical and health needs of patients requiring rehabilitation which must be met and that, if the physical handicap can be eradicated or minimized, the vocational potential will be increased. Reasons advanced for the employment of nonmedical directors include the fact that it may be difficult to secure a physician on a full-time basis and that sometimes physicians are not as competent as administrators and are not as able to foster the carrying out of the team concept as other professional personnel. In any event, whichever plan is adopted, it is our belief that the full-time participation of at least one physician is essential and that the medical and health needs of the patient must receive careful consideration in addition to the patient's other needs—social, psychological, educational, vocational, and recreational.

The handicapped patient has been referred to the rehabilitation facility to undergo any intensive program of maximum restoration in order that he might return home as independent and self-sufficient as possible. The rehabilitation center, in planning for this goal, should include the family physician in the conferences and planning regarding the patient. From the family physician the center can obtain the record of the patient's previous health. When the patient has completed his rehabilitation program he will return home and again be cared for by his family physician. If the family physician participates with the rehabilitation team during the rehabilitation program, he has a better understanding of the patient, his problems, and his potential and is better prepared to resume his care when he returns home.

The Program

While it is impossible in this paper to discuss all aspects of the program, certain areas of significance will be selected. It would be expected that each patient would be evaluated by the team on admission to the rehabilitation service, either as outpatient or as inpatient, and that the team members would discuss and make a plan for the patient. It would be expected that some one team member would be selected to interpret carefully the findings and recommended plan to the patient, his family, or both. Furthermore, it would be expected that the patient would be periodically reevaluated, perhaps every three to six months, in order that his program may be modified as indicated by his condition; this should apply to patients within the inpatient as well as the outpatient service. The reasons for periodic reevaluation of patients include the necessity of changing the program as the patients' needs change and the importance of a concerted effort to reduce unnecessary inpatient care when it is no longer warranted by the patients' condition, with its resultant reduction in patient costs and freeing of facilities for other patients.

Several methods exist for team functioning; included are the periodic team staff conference and the periodic team rounds. The former is usually conducted weekly and the latter daily but on a more abbreviated basis. All staff members attend and participate in the weekly staff conference, when, usually, service problems are discussed, policy decisions made, and certain patients reviewed (new admissions, those considered for discharge, those due for periodic review, and those with special problems). Many of the staff members attend daily rounds when the majority of patients are reviewed.

Surveys have indicated the importance of integrating the instruction given to patients in the various therapy departments with their activities during he rest of the day on the inpatient service. For example, if a patient is learning ambulation in the physical therapy unit, he should be given assistance and an opportunity to continue this when he is back in the floor nursing unit. This same principle applies to many other patient activities—dressing, toilet care, feeding, speech, tooth brushing, and others. In order to facilitate this, personnel employed in the floor nursing unit (nurses, attendants, and orderlies) must have reasonably good general technical skills and must have an intimate knowledge of the therapy program for each patient. It also implies a fundamental shift in concept of patient care on the part of personnel employed in the floor nursing unit from that of passive bed care to that of the patient's active participation in his own care.

Another aspect is integration of the vocational program with the other aspects of patient care—medical and health, social, psychological, and educational. This means that a vocational counselor will be an integral part of the staff of the rehabilitation service, actively participating in patient care with all teen-aged youths and adults known to the service. It also means that, whenever possible, the various steps of testing, guidance, training, and placement, as well as the sheltered workshop, should be a part of the rehabilitation service. Where the vocational aspects have not been so integrated, several undesirable results in patient care may occur—either there may be delay in referral of patients to the vocational agency or the vocational agency may be placed in the position of attempting to do testing, guidance, training, and placement without an adequate knowledge of the patient's physical and mental condition and capacity.

Patient records are essential, not so much in themselves but because they represent the one tangible source of description of the patient's course and response to the rehabilitation process, in contrast to dependence on man's memory and changing personnel. Thus, the patient's record should give a reasonably complete picture of himself and his family on admission, throughout his course, and at the time of separation from the service. The record should contain not only the medical and health data but also information regarding the patient's social, psychological, educational, and vocational status—both on an inpatient and on an outpatient basis. The data should be collected in a uniform manner on all patients, so that results in patient care may be analyzed.

Physical Plant

Special features of the physical plant include the floor nursing unit with nonskid floors, special bathroom facilities for easy wheel chair-to-toilet transfer, special kitchen facilities for teaching self-help, and service areas to be used jointly by the inpatient and outpatient services, including physical therapy, occupational therapy, speech therapy, psychological testing, and the vocational assistance areas with the sheltered workshop, in addition to offices for key personnel.

Ramps are considered essential where there is a change of floor elevation. Special unloading and reception areas for transportation vehicles are helpful. Where teachers are provided for children on inpatient services, classrooms are necessary.

Continuing Care of the Patient

Discharge planning and arrangements are an important step in the patient's rehabilitation. They include consideration of the family attitude, home conditions, details of the patient's continuing care and supervision, education of patients of school age, vocational guidance of youth and adults, and transportation. This discharge planning, to be effective, cannot take place only at the time of discharge. It must occur early and throughout the patient's rehabilitation course by maintaining close contact with the family, helping the family to accept the patient back into their family unit, assisting them with planning the details of the patient's 24-hour care at home if homebound, and planning facilities and equipment for such items as toilet care, wheel chair activities, and bathing. Frequently, both the social worker and the public health nurse play key roles, the former by close family contact within the rehabilitation service and the latter by working with the family at home. One of the crucial periods in the home care of the homebound patient is the first few days after the patient's discharge from the inpatient service—from the viewpoint of both the patient and his family. This particular period of stress is when some extra guidance and supportive services can be of great assistance until the adjustment within the home is made.

Unless a plan is made and carried through for the patient's continuing care and supervision, frequently he may receive little or no care and will regress. For this reason, details of the plan should be worked out prior to discharge and then carefully interpreted to the patient and his family. Periodic close supervision for the patient who is moderately to severely handicapped is essential. For the homebound patient, many communities have now worked out organized home care programs whereby the team of services is brought to the patient at home as he needs them. Organized home care programs have stemmed from a hospital, a medical school, a voluntary public health nursing agency, and a health department; it seems likely that they might stem from a rehabilitation service as well.

For the handicapped patient with a vocational potential, vocational evaluation and planning should be begun early in his rehabilitation program. In addition to psychological testing, prevocational evaluation may be desirable prior to placement in a vocational school or on the job. Many severely handicapped persons have had no work experience or have not been employed for many months. Their living habits are unsuitable for the demands of an occupation. A prevocational evaluation unit can provide a practical situation to check punctuality, personal cleanliness and neatness, ability to work with and tolerate others, speed and carefulness in work, and maintenance of interest in work. In the prevocational evaluation clinic, the level of ability of the patient can be established. The vocational counselor who has had an opportunity to work with a patient in his prevocational evaluation can place him with assurance of his level of performance.

Vocational placement of handicapped persons is usually a stressful situation. Most employers have some reservations about a handicapped employee. Plant physicians feel the personal insecurity that in accepting a handicapped employee they may be open to criticism if an accident occurs. Agents for

workmen's compensation insurance generally warn employers that they may be incurring increased risks and rates if they employ handicapped persons, even though all available statistics are contrary to this opinion. For this reason, the vocational counselor who makes the placement must make follow-up calls and visits to the employer and employee to see that the adjustment to the job and the performance of the job are satisfactory. For the employable patient, successful employment is the goal. None of the rehabilitation team, physician, therapist, counselor, or agency, can consider that a successful job of rehabilitation has been accomplished until the patient is satisfactorily employed.

Relationship to Other Community Agencies

On a cooperative basis, a rehabilitation service can carry out some other significant community functions. For example, in the case of adults, it can provide evaluation and diagnostic work for all patients applying for public assistance under the aid-to-the-disabled category and it can include in its rehabilitation program those patients found able to be rehabilitated. It can provide a similar service for youth and adults applying for vocational assistance under the state official vocational rehabilitation program. These two steps alone would mean earlier and more complete patient care with better results—and probably a considerable saving in tax funds. Similarly, the rehabilitation service can work cooperatively with the official crippled children's agency in reviewing the status of applicants for inpatient care and for special educational placement, such as home instruction, special schools, and special classes.

As public health programs begin to accept their responsibility in the chronic disease field, the need for public health personnel to receive training in this field will become more apparent. Here, too, the rehabilitation service is in a strategic position because of the training it can provide for health officers, public health nurses, nutritionists, and health educators.

Summary

A rehabilitation service should be located in a general hospital and care for many types of handicapped patients rather than limit the service to one or a few diagnostic groups. A full-time director, preferably a physiatrist, is desirable. Some aspects of the program include staff rounds and conferences, integration of therapy activities with the rest of the patients' care, integration of the vocational aspects into the other facets of rehabilitation, and recording of data. Continued care after discharge from the inpatient program is important.

Until more knowledge is available regarding primary prevention of many chronic diseases in both children and adults, rehabilitation services will be needed. The ultimate role which a rehabilitation service plays in the care of patients in a community will depend to a large extent on the soundness of the original planning and the staff's and community's concept of what it has to offer. Some of its role is also dependent on adequate financial support from the community, especially for the employment of the many kinds of professional personnel necessary in rehabilitation of patients.

CLINICAL NOTES

CYTOMETER CHAMBER SPERMATOCIDAL TEST

AN IMPROVED TECHNIQUE FOR EVALUATING SPERMATOCIDAL ACTIVITY

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Tests which measure the time required for varying concentrations of test substances to completely immobilize all spermatozoa in a given volume of spermatic fluid have been used in evaluating the relative spermatocidal activity of these substances.[1] Such dilutions are useful for measuring the intrinsic potency of an active ingredient in terms of minimal spermatocidal concentration, but the degree of homogenization required to provide reproducible results has no counterpart in coitus, and the relatively high values obtained are not applicable to defining the spermatocidal activity of contraceptive gels under conditions of use.

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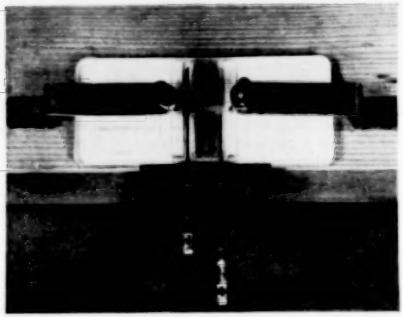
In order to approach normal conditions Gamble [2] devised a "diffusion test" for evaluating the spermatocidal activity of undiluted contraceptive products. The Gamble procedure utilizes glass tubing 2 cm. in length with an internal diameter of 2 mm. in which a column of semen is brought into contact with a column of undiluted contraceptive jelly, cream, or suppository mass. The observer measures the time required at 37 C for immobilization of spermatozoa in the sperm column as a result of diffusion of the active ingredients. The relatively small interface and long columns of materials result in prolongation of the time required for complete immobilization.

The diffusion procedure has been usefully modified by use of a Spencer "Bright-Line" hemacytometer instead of a capillary tube, with resultant reduction of time required for immobilization and a gain in reproducibility. The test procedure is described below, and the results are compared with those obtained by the capillary tube method in tests conducted concurrently on the same samples



Hemacytometer and cover glass secured in holding device. Needles inserted into lateral moats through holes in brass template for purpose of orientation.

of semen and spermatocides. The test procedure was greatly facilitated by use of a newly devised cytometer holder, which is described.

Materials and Method

The Spencer "Bright Line" hemacytometers, with improved double chamber and cover glasses, were used. The platforms of the six chambers used in this study varied from 6.0 to 6.2 mm. in width and were separated from each other by a moat 3.1 to 3.6 mm. wide. The cover glasses measured 19.1 to 19.8 mm. in width; hence, the length of platform covered was within that range, less the width of the moat. When the space between the platform and cover glass was filled with semen and the moats were filled with a spermatocidal preparation, the interface available for diffusion was 44 to 44.8 mm. in length by 0.1 mm. in depth, or 4.4 to 4.48 sq. mm. in area. The total volume of semen under observation was approximately 4.8 cu. mm.

Displacement of the cytometer cover glass during filling of the moats was avoided by use of the holding device illustrated in the figure. The holder consists of a wooden block equipped with a pair of adjustable spring clamps so spaced as to provide a downward thrust of the screws to hold the cover glass firmly in position when the cytometer is in place. The front of the block is provided with a brass template, 37 by 19 by 6 mm., through which holes have been drilled. These holes just permit passage of a 22-gauge hypodermic needle into each of the lateral moats of a cytometer slide. This device supports and guides the needle without risk of accidental displacement and facilitates uniform distribution of the injection mass.

Test Procedure.—The cover glass is held firmly in position and semen is run onto the open ends of the platforms until the areas under the cover glass are completely filled without overflow. The barrel of a tuberculin syringe fitted with a 22-gauge straight needle is filled with the spermatocidal preparation. The needle is then inserted through the brass template into one lateral moat, and the area of the moat under the cover glass is filled as the needle is slowly withdrawn along the moat until the transverse moat is reached. The needle is halted at the open edge of the transverse moat with the needle opening directed toward the moat and the material is extruded until the transverse moat is completely filled; the remaining portion of the lateral moat is then filled as the needle is slowly withdrawn. The other lateral moat is completely filled with the test material in the same manner. Both ends of the cover glass and the ends of both lateral moats are sealed with petrolatum jelly to prevent concentration by evaporation. Microscopic examination for evidence of motility of spermatozoa is started as soon as the preparation is completed and is continued at frequent intervals. Spermatocidal time is recorded as the time from the filling of the moats with the contraceptive material until all spermatozoa under the cover glass, in both chambers, have been immobilized at room temperature (74 to 78 F).

Gamble's capillary tube diffusion test and the cytometer chamber test procedure were used concurrently to determine the spermatocidal times of several commonly used contraceptive products and a new formulation (Lanesta gel) designed for the same purpose. The products in the accompanying table are listed in increasing order of their respective mean spermatocidal times. Spermatic fluids were provided by six young healthy donors aged 23 to 37 years. Ejaculates were submitted early in the morning and used within one to four hours of submission. On any one day only one specimen of spermatic fluid was usually used, as from one to four tests were run on each contraceptive preparation. Several samples of spermatic fluid were obtained from each donor over a period of weeks. Inasmuch as specimens differed from source to source and even ejaculates from the same donor were not always comparable in respect to percent-

In Vitro Spermatocidal Acticity of Six Contraceptive Jellies

Jelly	Cytometer Chamber Spermatocidal Test		Gamble Capillary Tube Test	
	No. of Tests	Mean Spermatocidal Time ± S.E., Min.*	No. of Tests	Mean Spermatocidal Time ± S.E., Min.*
A†	40	31.9±0.7	28	50.6± 2.3
B	41	90.0±2.8	49	206.1±11.9
C	50	104.0±6.0	61	217.3±12.1
D	36	110.6±3.6	53	236.3± 9.5
E	28	174.0±7.3	53	262.7±11.8
F	28	259.1±9.8	51	313.3±10.3

* S.E.=standard error of the mean.
† Lanesta gel.

age of viability and degree of motility of spermatozoa, each specimen of spermatic fluid was tested at the same time by both methods and against each preparation in order to compensate for differences which might result from the testing of different ejaculates. Each contraceptive was tested as many as 28 to 50 times by the cytometer chamber procedure and 28 to 61 times by Gamble's capillary tube diffusion procedure.

Results.—By the cytometer chamber diffusion test the new spermatocidal formulation, jelly A (Lanesta gel), immobilized spermatozoa in one-third the time required for any of the three other most active products (jellies B, C, and D), and in one-fifth the time required for jelly E and in one-eighth the time required for jelly F. The absolute figures for each are given in the table in terms of mean spermatocidal times. By Gamble's capillary tube test, jelly A demonstrated a correspondingly wide margin of superiority over the other products tested.

Comment

The use of procedures for measurement of spermatocidal time which involve dilution and/or mixture of contraceptive with spermatic fluid is unsatisfactory because neither the required degree of mixing nor the extent of dilution has any counterpart under conditions of use. Moreover, reproducibility is difficult to achieve in tests which require mixing but do not require dilution. In Davidson's test [3] spermatozoa cannot be readily seen except in certain irregular areas, because of the opacity of some preparations; also this test requires the use of nonviscous semen. By the Sander-Cramer [4] and Millman [5] saturation tests, the time element for mixing of jelly and semen, preparation of slide, and examination of several fields under the microscope is so short (20 seconds) that duplication of test results is difficult and subject to wide variation. In addition, these tests often require several milliliters of semen per test, depending on the activity of the preparation. Thus, repetition of the test and simultaneous comparison with other preparations using the same ejaculate is seldom possible. The authors of these tests recommend the use of nonviscous spermatic fluid and admit that results are not always reproducible with "sticky" samples. Millman's "zone" test [5] claims to measure the penetration of spermatozoa into the contraceptive preparation. Gamble [2] pointed out in discussing Millman's procedure that the high dilutions used in the zone test and the short distances traversed by spermatozoa indicate that penetration into undiluted jelly or cream is nonexistent or minimal. By direct methods of observation, such as the present cytometer chamber spermatocidal test method, in which it is possible to observe every single spermatozoon in the preparation, we have never observed active penetration of spermatozoa into any undiluted contraceptive.

There is no factual basis for the assumption that there is any marked degree of dilution of a contraceptive in the vagina by vaginal secretions. The average volume of vaginal secretion after copulation was postulated [1] to be approximately 1 ml., whereas the usual volume of contraceptive jelly or cream that is introduced into the vagina is 5 ml.; therefore the greatest possible source of dilution is seminal fluid, which rarely exceeds 5 to 7 ml. Under these conditions, dilution of jelly or cream is likely to be 1:1 or maximally 1:2. Also, contraceptive preparations are characteristically either hydrophobic, because of fatty ingredients in the formula, or they are gelled with gums which are not readily miscible and which require time for imbibition of water. In view of the fact that spermatozoa cannot be depended on to actively penetrate into a jelly or cream, the best alternative to thorough mixing by artificial methods is dependence on diffusion of spermatocidal constituents into the spermatic fluid. The cytometer diffusion procedure described herein offers a convenient, reproducible method of measuring this diffusibility and of predicting the clinical effectiveness of a contraceptive jelly, cream, or suppository mass.

Summary

A new test procedure, designated the cytometer chamber spermatocidal test, for determining the speed of spermatocidal action of contraceptive products is a modification of Gamble's diffusion test, with use of a double chamber hemacytometer instead of capillary tubes.

The new test procedure is simple to carry out. The range of variations from one test to another falls within narrower limits than the Gamble diffusion test. The over-all time required for spermatocidal action is shorter by the new procedure than by the Gamble test.

A new contraceptive formulation was found to immobilize human spermatozoa in one-third to one-eighth the time required by five of the leading contraceptive products currently available.

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Mr. K. T. Krantz helped to devise the cytometer holder.

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CLINICAL EVALUATION OF THE STARCH TOLERANCE TEST

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Early diagnosis of chronic benign or malignant disease of the pancreas is a problem that has haunted physicians for many years. In spite of rather startling advances made in other fields, clinical evaluation and a high index of suspicion continue to be the mainstays in the diagnosis of these diseases. Several new laboratory tests or modifications of older tests have been put to trial, the starch tolerance test described by Althausen and Uyeyama[1] being one of these. We have attempted to evaluate this test clinically.

The starch tolerance test is based on the premise that pancreatic amylase is the only significant physiologic enzyme responsible for the breakdown of starch into disaccharides. In this form it is absorbed by the intestinal tract. The original authors found that 87% of all patients with chronic benign and malignant disease of the pancreas showed abnormal results on starch tolerance tests. Kalser and coworkers[2] in evaluating the starch tolerance test found an accuracy of 69% in proved cases of pancreatic disease. With these facts in mind we felt that the test should be evaluated with regard to its relative merit in the diagnosis of pancreatic disease.

Materials and Methods

Sixty-eight patients were studied in the department of gastroenterology at the Lahey Clinic. In all cases pancreatic disease was suspected clinically. Studies included history, physical examination, routine laboratory tests, gastrointestinal x-rays, and such further studies as were deemed necessary for their clinical evaluation.

All patients were given a starch tolerance test by the method of Althausen and Uyeyama, with use of either United States Pharmacopia corn starch or chemical "soluble starch." In all cases the starch was prepared under the supervision of one of us (F. W. N.). This was done because of the known difficulty in preparation and also to encourage rapid ingestion by the patients of this distasteful mixture. Although saccharin and small amounts of lemon juice were used, we were unable to produce a palatable mixture.

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The maximal rise in blood sugar level after the oral ingestion of glucose was compared to the rise after oral ingestion of starch and calculated as suggested by the original authors. All results over 100% were considered abnormal, while those under 100% were accepted as being within the normal range.

Results

Of the 68 cases studied, in 50 (cases 1-50) the final diagnosis was some condition other than pancreatic disease. These conditions included functional disease of the gastrointestinal tract, infectious hepatitis, duodenal ulcer, gastric ulcer, cholelithiasis, retroperitoneal malignant disease not originating in the pancreas, renal cysts and neoplasms, malabsorption syndrome, segmental jejunitis, and hiatus hernia.

In 46 of these cases, the starch tolerance test gave negative results, and in 4 the results were positive. One patient (see table, case 45) had proved metastatic malignancy in a lymph node; this obstructed the ampulla of Vater and therefore the test results cannot be considered false-positive. The results in the other three cases, however, must be considered false-positive. One patient (case 44) had infectious hepatitis, but exploration for suspected carcinoma of the head of the pancreas revealed a normal pancreas. Three other patients with infectious hepatitis had negative results on starch tolerance tests. In one patient (case 24), the absorption of glucose was early and rapid. Within the first half-hour the blood sugar level rose 119 mg. per 100 cc. after ingestion of glucose, whereas it rose only 29 mg. per 100 cc. in a similar period after ingestion of starch. This probably explains the false-positive test. This patient was seen two years later and showed no clinical evidence of pancreatic disease. The other patient (case 29) had cholelithiasis and results of the test were false-positive.

Twelve patients (cases 57-68) had chronic relapsing pancreatitis, as proved at surgical exploration. The starch tolerance test gave positive results in eight of these cases; in four the results were negative. Thus, in cases of chronic benign disease of the pancreas, the over-all accuracy was 66.6%. The glucose tolerance test showed positive results in seven of these cases (58.3%).

Six cases of carcinoma of the pancreas are included in the group (cases 51-56). The presence of carcinoma was proved at operation in all these cases. In only one case (case 55) did the starch tolerance test show positive results, while in the other five the results were within normal range. The pancreas, since the diagnosis was not proved. The starch tolerance test gave negative results in both instances.

In all, 18 of the 68 patients in the series proved to have pancreatic disease. In only nine of these cases did the starch tolerance test show positive

Summary of Results in Sixty-Eight Patients Given Starch Tolerance Test

Case, No.	Final Diagnosis	Starch Test, %	Remarks
1	Functional gastrointestinal disease	32	Abdominal pain
2	Functional gastrointestinal disease	2	Abdominal pain
3	Functional gastrointestinal disease	0	Abdominal pain and vomiting
4	Functional gastrointestinal disease	0	Abdominal pain and diarrhea; latent diabetes
5	Functional gastrointestinal disease	37	Healed pyloric ulcer and gallstones; latent diabetes
6	Functional gastrointestinal disease	0	Abdominal pain
7	Functional gastrointestinal disease	73	Abdominal pain
8	Functional gastrointestinal disease	9	Abdominal pain
9	Functional gastrointestinal disease	54	Pain in left side of chest; ? enlargement in head of pancreas on x-ray
10	Functional gastrointestinal disease	3	Abdominal pain
11	Functional gastrointestinal disease	0	Abdominal pain; latent diabetes
12	Functional gastrointestinal disease	0	Abdominal pain
13	Functional gastrointestinal disease	0	Abdominal pain
14	Functional gastrointestinal disease	2	Abdominal pain
15	Functional gastrointestinal disease	0	Abdominal pain
16	Functional gastrointestinal disease	0	Back pain; weight loss
17	Functional gastrointestinal disease	0	Abdominal pain; latent diabetes
18	Functional gastrointestinal disease	27	Abdominal pain
19	Functional gastrointestinal disease	0	Weakness; weight loss
20	Functional gastrointestinal disease	32	Abdominal pain; latent diabetes
21	Functional gastrointestinal disease	60	Abdominal pain; nausea
22	Functional gastrointestinal disease	74	Healed gastric ulcer; abdominal pain; latent diabetes
23	Functional gastrointestinal disease	40	Abdominal pain; latent diabetes
24	Functional gastrointestinal disease	310	Abdominal pain; rapid absorption of glucose
25	Cholelithiasis	1	Abdominal pain
26	Cholelithiasis	69	Weight loss; anorexia
27	Common duct stone	0	Abdominal pain
28	Common duct stone	21	Abdominal pain; latent diabetes
29	Cholelithiasis	138	Abdominal pain; latent diabetes
30	Cholelithiasis	54	Abdominal pain
31	Segmental jejunitis	63	Abdominal pain; segmental jejunitis on x-ray; latent diabetes
32	Intermittent obstruction of small intestine	0	Abdominal pain
33	Hiatus hernia	72	Abdominal pain; latent diabetes
34	Hiatus hernia with regurgitation; esophagitis	25	Regurgitation and vomiting; weight loss
35	Duodenal ulcer	0	Abdominal pain
36	Duodenal ulcer	0	Abdominal pain
37	Duodenal ulcer	0	Right upper quadrant pain
38	Left renal cyst	0	Mid-abdominal pain
39	Left renal cyst	0	Abdominal pain; abdominal mass on left side; latent diabetes
40	Malabsorption syndrome	60	Diarrhea of 18 months' duration
41	Hepatitis	97	Abdominal pain; jaundice; diabetes mellitus
42	Infectious hepatitis	66	Jaundice; x-ray—question of enlargement of head of pancreas; latent diabetes
43	Gastric ulcer; hepatitis	0	Abdominal pain; diarrhea; latent diabetes
44	Hepatitis	559	Vomiting with weight loss; latent diabetes
45	Metastatic carcinoma of colon	139	Mass involving duodenal area and invading ampulla of Vater; latent diabetes
46	Malignant melanoma	0	Retroperitoneal involvement with metastasis to liver; latent diabetes
47	Adenocarcinoma of bile ducts	11	Abdominal pain
48	Retroperitoneal malignancy with metastasis to lungs	79	Abdominal pain; latent diabetes; mass located in pancreatic area, probably representing pancreatic carcinoma but not proved
49	Metastatic malignancy	0	Abdominal pain; latent diabetes; x-ray evidence of mass in pancreatic area, scalenus node positive for carcinoma
50	Carcinoma of the left kidney	30	Weight loss; anorexia
51	Carcinoma of the pancreas	9	Back pain; weight loss; latent diabetes
52	Carcinoma of the pancreas	36	Abdominal pain; latent diabetes
53	Carcinoma of the pancreas	14	Abdominal pain; weight loss; latent diabetes
54	Carcinoma of the pancreas	0	Abdominal pain
55	Carcinoma of the pancreas	100	Abdominal pain; latent diabetes
56	Carcinoma of the pancreas	0	Right upper quadrant pain; anorexia; diabetes mellitus
57	Chronic relapsing pancreatitis	0	Abdominal pain; weight loss; latent diabetes; pancreatic calcifications
58	Chronic relapsing pancreatitis	91	Abdominal pain; latent diabetes; pancreatic calcifications
59	Chronic relapsing pancreatitis	35	Abdominal pain; vomiting; latent diabetes; pancreatic calcifications
60	Chronic relapsing pancreatitis	226	Abdominal pain
61	Chronic relapsing pancreatitis	0	Abdominal pain; vomiting
62	Chronic relapsing pancreatitis	1,850	Abdominal pain; pancreatic cyst
63	Chronic relapsing pancreatitis	200	Abdominal pain; nausea; vomiting
64	Chronic relapsing pancreatitis	140	Abdominal pain; fever
65	Chronic relapsing pancreatitis	173	Abdominal pain; latent diabetes
66	Chronic relapsing pancreatitis	Inf.	Abdominal pain; latent diabetes
67	Chronic relapsing pancreatitis	105	Abdominal pain; latent diabetes
68	Chronic relapsing pancreatitis	165	Abdominal pain; latent diabetes

glucose tolerance test showed positive results in five (83.3%). Two other patients (cases 48 and 49) had the picture of carcinoma of the pancreas clinically and roentgenologically. Lung metastases were present in one and metastases to the supraclavicular lymph nodes in the other. Neither was included among the group of patients with cancer of the results. Thus, the over-all accuracy was only 50%. In three instances the test results were false-positive.

Of the 68 patients, 30 had latent diabetes. This condition was defined in our study by a blood sugar level exceeding 140 mg. per 100 cc. two hours after ingestion of glucose. In 12 (66%) of the 18 proved

cases of pancreatic disease, latent diabetes was also present. In the 50 patients who did not have pancreatic disease, 18 (36%) had latent diabetes, including 3 of the 4 patients with infectious hepatitis.

In all patients with pancreatic disease, multiple abdominal roentgenograms were taken; these were carefully studied for evidence of calcification in the pancreatic area. Of the 12 patients with chronic relapsing pancreatitis, calcification was found in three instances. Calcification was not noted in any of the six cases of carcinoma of the pancreas.

Comment

The pancreas has two major physiological functions: the endocrine and the exocrine. The endocrine function can be assessed fairly accurately by the glucose tolerance test, a well-established method. Tests of exocrine function, unfortunately, are not as accurate. These can be roughly divided into two groups: tests of acinar function and tests of ductal cell function. Excretion of bicarbonate and water by the ductal cells is the basis of the secretin test.[3] Acinar function is determined by the enzymatic secretions reaching the blood or small intestine. Amylase and lipase determinations, the gelatin tolerance test,[4] the starch tolerance test, radioactive-labeled protein[5] and radioactive-labeled fat[6] studies all attempt to evaluate this function.

Normal pancreatic exocrine function is, of course, a combination of these actions. Acinar cells must be present to secrete the enzymes and a patent ductal system is necessary to deliver them to the intestine. It is well known that the pancreas has a tremendous reserve capacity and that a large portion of the gland may be destroyed without producing significant abnormality in the over-all pancreatic function.

The starch tolerance test is based on a comparison of the ability to absorb orally administered glucose to the ability to absorb orally administered starch. This, in turn, is based on the theory that pancreatic amylase is the only physiologic substance capable of hydrolyzing starch in significant amounts.

Salivary amylase, gastric hydrochloric acid, hydrolyzing substances secreted by the small intestine, and bacterial fermentation in the intestine are capable of producing degrees of starch hydrolysis. That these factors can influence this test is well attested to by the case of Kalser and co-workers.[2] In this case a patient who had undergone total pancreatectomy showed an elevation of the blood sugar level from 200 mg. per 100 cc. to 422 mg. per 100 cc. after the ingestion of starch.

The transit time of food from stomach to colon (particularly for cases in which segments of the upper gastrointestinal tract have been resected) and malabsorption or unusually rapid absorption of glucose can obviously be modifying factors.

Our results with this test would indeed seem discouraging. In all instances, proved pancreatic disease was strongly suspected preoperatively on the basis of evaluation of the clinical course, glucose tolerance, roentgenographic findings, and other evidence. In no case was the starch tolerance test instrumental in solving the problem.

In one patient (case 57) the duct of Wirsung was completely obstructed by a calculus 3 cm. distal to the ampulla of Vater, yet the starch tolerance test gave negative results. In another patient (case 62), however, with cyst formation and pancreatitis localized to the tail of the pancreas, the starch tolerance test gave strongly positive results in spite of the fact that the proximal two-thirds of the gland was quite normal.

The most disturbing aspect of this study is its failure to provide a means of diagnosing carcinoma of the pancreas. This is one of the most difficult challenges we must face. Despite the fact that in each of our six cases the diagnosis was strongly suspected clinically, only one patient showed positive results on the starch tolerance test.

Certainly all efforts must be directed to the search for means of early diagnosis of pancreatic disease. We do not feel, however, that the starch tolerance test is the answer.

Summary

The starch tolerance test was performed on 68 patients in whom pancreatic disease was suspected. Of the 18 patients with proved disease, 9 (50%) had positive results on the starch tolerance tests. Only one patient with proved carcinoma of the pancreas showed positive results on starch tolerance test, whereas the results were negative in the other five. We do not believe this is a reliable test for the detection of pancreatic disease, on the basis of the studies described in this report.

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CORNEAL COMPLICATION OF CHLOROQUINE (ARALEN) PHOSPHATE THERAPY

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Alteration of the corneal epithelium causing blurred vision occurred in 10 patients taking chloroquine (Aralen) phosphate, which is currently being used for a variety of diseases including malaria, lupus erythematosus, arthritis, and infestation with intestinal parasites. Chloroquine has a low incidence of toxicity. However, the corneal changes resulting in some patients taking the drug lead to symptoms (haloes around lights and blurred vision) suggestive of glaucoma. The change in the corneal epithelium varied from diffuse discrete white depositions to yellowish discrete dots grouped at the level of the epithelium and Bowman's membrane. The configuration of the depositions was diffuse in some cases, but most were linear. The maximal involvement was usually in the central portion of the cornea, with the area just below the pupil showing the greatest concentration.

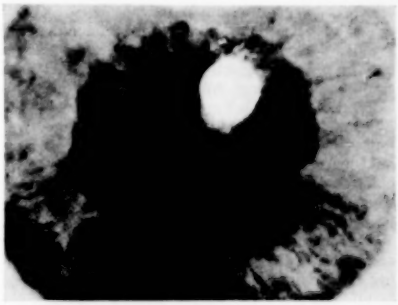
Some of the patients did not have any complaints about their vision. However, four sought ophthalmological help because they saw haloes around lights at night. All four had been told nothing was wrong and it had been intimated that they were suffering from "nerves." This diagnosis was made because the change is a slight one and careful examination with the biomicroscope (slit-lamp) is necessary to see the alteration in the cornea. When the disease is further advanced it is quite easy to see the pigment deposits. Reduction of visual acuity was not seen even though patients complained of blurring of their vision. When these patients were tested with Snellen charts their visual acuity was not lower than it had been prior to drug therapy. In some cases the granular appearing deposits became quite dense and assumed a more or less yellowish appearance. The density of the opacification of the cornea does not seem to be definitely related to the amount of drug taken. A patient taking 1,000 mg. of chloroquine daily for three years showed less change than one taking 250 mg. daily for nine months (see figure).

Twenty-two patients exhibiting the same corneal changes were described by Hobbs and Calnan.[1] In most of their cases, the corneal abnormalities regressed when the drug therapy was stopped. Our cases showed the same happy results occurring two to four months after therapy was stopped. However, Hobbs and Calnan reported one case in which visual acuity continued to decrease even after therapy was stopped.

Corneal changes of a different nature (edema of the corneal epithelium) have been reported in patients taking quinacrine (Atabrine) hydrochloride which is chemically related to chloroquine.[2] No edema was seen in our patients or was reported by Hobbs and Calnan.

Yellow staining of the conjunctiva and cornea occurred in workers in contact with quinacrine dust in a factory where the drug was manufactured. The staining was interpreted as actually representing the drug itself.[3] No conjunctival involvement was seen in our patients and the blue haloes seen by quinacrine workers are different from the blurred vision and haloes noted by patients taking chloroquine.

There is evidence chloroquine is widely stored in the structures of the body. In two of our most severely involved cases the patients appeared to have a faint fluorescence of the involved cornea when exposed to the Wood's light (ultraviolet).



Linear and diffuse pigment deposits in central corneal epithelium of 48-year-old woman treated with chloroquine for arthritis (250 mg. daily for nine months).

This possibly indicates that it is the drug itself which is deposited in the corneal epithelium because the drug does fluoresce. In less involved cases there is no fluorescence. It is too early to state whether or not chloroquine is stored in the lens epithelium, but this seems a definite possibility.

Summary

Ten patients exhibiting discrete opacification of the corneal epithelium were taking chloroquine (Aralen) phosphate for arthritis or lupus erythematosus. The changes appear to be reversible on cessation of the drug therapy. Not all patients complained of visual problems but all showed corneal abnormalities with the biomicroscope. Some noted haloes around lights, a symptom which may lead to a mistaken diagnosis of glaucoma.

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PURPURA DUE TO CHLOROTHIAZIDE (DIURIL)

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Chlorothiazide (Diuril) is an orally administered, nonmercurial, diuretic agent. Chemically, it is known as 6-chloro-7-sulfamyl-1,2,4-benzothiadiazine-1,1-dioxide.[1] It was made available commercially only this year; but, in its use thus far reported, the absence of toxic and otherwise undesirable side-effects has been especially noted.[2]

Ten of 51 patients observed by Hollander and Wilkins [2a] experienced slight to moderate weakness and fatigability, which usually disappeared with continuous treatment. In several, this weakness was associated with a feeling of mental depression, and, in a few of these, the level of serum potassium was reduced. Five patients complained of temporary mild nausea, especially when given 500 mg. of chlorothiazide in single doses. Other uncommon side-reactions included muscle cramps, flushing, lightheadedness, and paresthesias.

The potential development of clinical symptoms and signs of fluid and electrolyte imbalance resulting from chlorothiazide therapy has been stressed by all investigators.[2]

So far as we know, purpura resulting from the administration of chlorothiazide has not been reported in the literature. Two patients with such effects have been seen recently at the Mayo Clinic, and their cases are described here.

Report of Cases

Case 1.—A 66-year-old man was seen because of an eruption of two weeks' duration on his legs. The patient said he had taken chlorothiazide for one month several months before being seen at the clinic but had stopped for no definite reason. Two weeks before the present examination, he began again to take the drug, 500 mg. twice a day. Within two days after resuming chlorothiazide therapy, he noted the appearance of a petechial eruption about both ankles with subsequent involvement of the dorsa of the feet and hands and the distal half of both lower legs. The patient had continued to take chlorothiazide up to the time he was seen at the clinic. He denied bleeding from any of the body orifices or the gums. Four years previously he had given a history of easy bruising and prolonged bleeding, though examination at that time was nonrevealing. He denied the use of other drugs.

The patient was admitted to the hospital. The pertinent dermatological findings consisted of a confluent, symmetrical purpura involving the ankles and lower half of both legs. There were scattered petechiae involving the dorsa of the feet and hands. The patient also had keratoderma of the palms and soles and intertrigo of the inguinal areas. Hematological examination, including tests of the bleeding and clotting mechanisms, gave results within the limits of normal.

The patient was treated with bed rest and diphenhydramine (Benadryl) hydrochloride. The use of chlorothiazide was discontinued. During 10 days of hospitalization, 85% of the purpura cleared with no new lesions appearing during that time.

Case 2.—A 70-year-old man with congestive heart disease had been a patient at the clinic for many years. He had been receiving mercaptomerin (Thiomerin) sodium for three years and digitoxin preparations and ammonium chloride for two years. In January, 1958, he had been instructed to take chlorothiazide, 500 mg. twice daily three times a week.

In June, 1958, the patient showed dermatosis on his hands. Examination at this time revealed petechiae and purpura symmetrically distributed on the dorsa of the hands and about the ankles. Hematological examination, including tests related to the bleeding and clotting mechanisms, gave results within normal limits except for a count of only 94,000 platelets per cubic millimeter of blood. Continued use of digitoxin and ammonium chloride was advised, but chlorothiazide and mercaptomerin were no longer prescribed.

During the next week the amount of purpura and number of petechiae increased, with spread of the lesions to involve the lower half of the legs and the forearms. The patient's condition merited the use of mercaptomerin, and this was given without obvious increase in the severity of the purpura.

During the next two weeks, there was complete resolution of the petechiae and purpura. Throughout this time, digitoxin, ammonium chloride, and mercaptomerin were administered without apparent toxic effect. Their use has been continued to the time of writing without recurrence of purpura. Reappearance of purpura followed promptly, however, after chlorothiazide was given again in a single dose of 500 mg.

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Summary

Previously reported undesirable side-effects of chlorothiazide (Diuril) therapy have been primarily those related to fluid and electrolyte imbalance.

At this clinic, two cases of purpura resulted from the administration of this drug.

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COUNCIL ON FOODS AND NUTRITION

METABOLIC AND BIOCHEMICAL CHANGES IN NORMAL PREGNANCY

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The following is one of the six papers presented at the symposium on "Nutrition in Pregnancy" in Columbia, Mo., Oct. 11, 1957. This symposium was sponsored by the Council on Foods and Nutrition with the cooperation of the Boone County Medical Society, the University of Missouri School of Medicine, and the Adult Education and Extension Service of the University of Missouri.

PHILIP L. WHITE, SC.D., *Secretary.*

Many inherent metabolic and biochemical changes occur at the time of and after conception. Gestation presents three recognizable phases: (1) the preimplantation period that extends for approximately two weeks after conception; (2) the two-to-eight-week interval during which major organogenesis takes place; and (3) the period of most rapid prenatal and maternal growth, which extends from about eight weeks to term.

Metabolic and Functional Changes in Pregnancy

The implantation of the fertilized ovum causes the regulatory and functional mechanisms of the body to be thrown out of balance and results in a disturbed physiological state. The effects are observed in upsets in the gastrointestinal system—a decrease in appetite resulting in reduced food consumption, and nausea, sometimes with vomiting, which may result in a loss in weight. The results of metabolic changes may be seen in the level or distribution of blood components, in the level of urinary components, in the retention of nutrients, in the composition and function of the blood cells, in hormonal secretions, and in the composition and function of the placenta.

Alterations in Hormonal Secretions.—The three hormones primarily concerned in reproduction are the gonadotropins, the estrogens, and progesterone.[1]

From the Merrill-Palmer School.

Gonadotropins can be detected in the serum and in the urine a few days after the first missed menstrual period and continue to increase rapidly, reaching the maximum in about 50 to 70 days. They are believed to work in conjunction with the corpus luteum, causing it to persist and play a dominant role in organogenesis and growth of the fetus until about the fourth month of pregnancy. At the height of production, the gonadotropins may be excreted at a rate of 40,000 to 200,000 rat units per 24 hours. This level of excretion is maintained for a short time; by the 110th to the 120th day, it decreases to 5,000 to 10,000 rat units per 24 hours, a level maintained until the end of pregnancy. In cases of disturbed gestation, a late rise in both serum and urinary gonadotropins may occur. Biological tests of pregnancy depend on the presence of gonadotropins.

Progesterone, the corpus luteum hormone, is secreted until the third or fourth month of pregnancy. It stimulates the occurrence of secretory changes in the endometrium in preparation for the implantation of the fertilized ovum about the sixth day of the luteal phase of the ovum. By the third week of gestation, the placenta has grown and has developed to the point of initial functioning, producing some progesterone. Increased growth and function of the young metabolically active placenta permit it to take over the formation of progesterone between the second and third months of gestation, thus continuing the conditioning of the endome-

trium to provide for the nourishment of the conceptus. The reduction of progesterone is measured by its metabolites, pregnanediol and pregnanolone, and it is excreted as glycuronides of these substances. Maximum secretion is usually reached around the 220th to the 240th day. At term, values of the pregnanediol complex may fall between 50 and 100 mg. per 24 hours. After delivery, this hormone disappears rapidly from the urine.

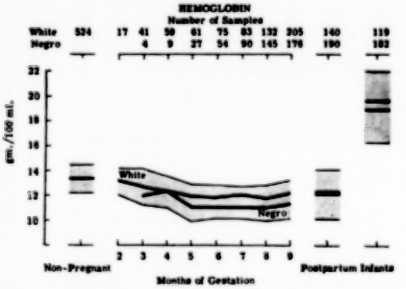

Fig. 1.—Trend of median hemoglobin levels of white, nonpregnant women, of selected white and Negro women during gestation and after delivery, and of their respective newborn, term infants. The 10th-90th percentile range for combined racial groups serves as standard for normality.

The pattern of estrogen level is similar to that of pregnanediol, low in early pregnancy with a slow increase through gestation. It does not increase appreciably until about the 100th day, with the greatest increase occurring in the last half of pregnancy, reaching values of 40,000 to 50,000 mcg. per 24 hours and attaining its maximum about 10 days before delivery. Estrogen and progesterone are maintained at high blood concentration levels during pregnancy; they stimulate growth and functional changes in the breasts and suppress the lactogenic function of the pituitary gland until delivery, when the pituitary gland stimulates the mammary glands to secrete milk.

The alteration in steroid metabolites during normal pregnancy has provided a valuable index of the adaptation of the adult organism to pregnancy.[1] The ketosteroid components in the urine of pregnant women differ quantitatively and qualitatively from those found in the urine of nonpregnant women. Of the 19 ketosteroids that have been characterized, 11 have been found in the urine of pregnant women. These observations furnish evidence that pregnancy induces alterations in the mechanisms of production or metabolism of the steroid precursors.

Placental Development.—During pregnancy, the growth rate of the placenta does not parallel that of the fetus, since the former attains its maximum size early in gestation. In the seventh month of pregnancy, the ratio of fetal weight to placenta weight is about 3.7:1; at term it has increased to 7.5:1. The wet weight of placentas ranges from 325 to 1,000 Gm., with an average of about 580 Gm. Large birth weights are not indicative of large placentas.

The placenta is essentially an organ with a nutritional function; it is well supplied with carbohydrate, protein, fat, enzymes, hormones, and minerals. Though there is a dearth of information about the progressive changes in the chemical composition of the placenta, under normal conditions its chemical composition during gestation varies to suit the demands made on it by the growing fetus. For example, the fat and carbohydrate contents are reduced in the last quarter of pregnancy; the vitamin content of the placenta increases during the course of pregnancy and then decreases near its termination.

Fetal nutrition depends, to a large extent, on the efficiency of the transmission of material across the placental barrier. The area of contact between maternal and fetal circulations has been estimated as between 10 and 13 sq. m. Only materials that can be carried in solution by the blood and can pass through the semipermeable wall of the chorionic villi can penetrate this barrier. Proteins of large molecular structure, with the exception of antibodies, are not transferred, whereas amino acids and proteoses are. Fetal fat is synthesized from

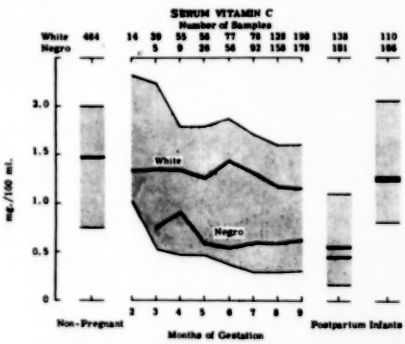

Fig. 2.—Trend of median serum vitamin C levels of white nonpregnant women, of selected white and Negro women during gestation and after delivery, and of their respective newborn, term infants. The 10th-90th percentile range for combined racial groups serves as standard for normality.

lipid components passed from the mother's blood to that of the fetus. Chemically it is quite different from the body fat of the mother; fetal fat is richer in palmitic acid and contains less oleic and stearic acids. Vitamin D, ascorbic acid, thiamine, and

riboflavin are present in the human placenta [3] and are passed through it in regulated amounts. Vitamin A and carotene are passed through the placenta in less regulated amounts.

The placenta may well be considered an endocrine gland, since hormones similar to those of the pituitary gland have been demonstrated and since endocrine functions of the ovary are duplicated. Needham [3] pointed out the high content of ascorbic acid in the corpus luteum and the fact that it paralleled progesterone; he then assumed that ascorbic acid may be necessary to the production of the hormone. Values for ascorbic acid in the corpora lutea of nonpregnant women range from 24.8 to 48.3 mg. per 100 Gm.; for women in the second to fifth month of pregnancy, the values are 42.3 to 148.7 mg. per 100 Gm. The ascorbic acid content of the placenta is greater in the early months of pregnancy when its metabolic activity is greatest. The ascorbic acid content of an infant at birth averages 38 mg. per 100 Gm. of tissue; it decreases to 10.8 mg. per 100 Gm. during the first four months after birth. Excretion of ascorbic acid in the urine of the newborn infant [4] would indicate that there must be a plethora of this vitamin for fetal growth and development.

At the fourth month of development, the fats and lipids of the placenta are present in greater quantity in relation to the weight of the fetus than at any other time. In the developing placenta, there is disintegration of the lipids, releasing fatty acids, phosphorus, and choline. In comparison with values of other tissues, niacin is the only one of the B vitamins that is present in relatively large amounts.

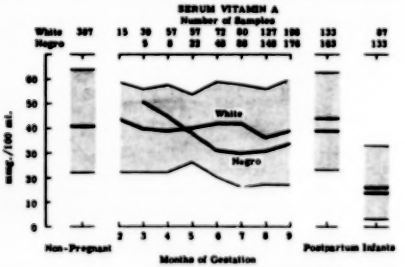

Fig. 3.—Trend of median serum vitamin A levels of white nonpregnant women, of selected white and Negro women during gestation and after delivery, and of their respective newborn, term infants. The 10th-90th percentile range for combined racial groups serves as standard for normality.

Basal Metabolism.—The basal metabolic rate falls from a normal to a subnormal level during the third to the fourth month of gestation. From this point, a steady increase is noted that amounts to 13% or more in excess of the rate conditioned by the gross increase in body weight. The basal metabolic rate does not differentiate between the tissues with high metabolic activity, such as the placenta, the fetus, and organs of both mother and fetus, that are more active than others. Basal metabolism is also influenced by increased thyroid function, as demonstrated by the steady increase of blood iodine from the second to the tenth month and by a decrease in blood iodine in the first two weeks of puerperium. Anatomic studies of thyroid glands obtained at autopsy from pregnant women [5] reveal larger follicles with abundant colloid and, at the same time, definite signs of cellular hypertrophy when compared with thyroids from nonpregnant women. Experimental studies suggest a greater need for thyroid hormone during pregnancy.

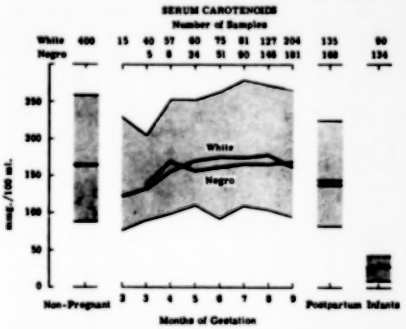

Fig. 4.—Trend of median serum carotenoid levels of white nonpregnant women, of selected white and Negro women during gestation and after delivery, and of their respective newborn, term infants. The 10th-90th percentile range for combined racial groups serves as standard for normality.

Other Hormonal Implications.—Loss of appetite, reduction in food intake, and disturbed gastrointestinal equilibrium in the preimplantation and organogenesis phases of pregnancy may well result from the excessive amounts of certain hormones elaborated by these glands [6] and from the morphologic and functional changes which they bring about in the digestive tract. The efficiency of absorption and of enzyme production is dependent on hormonal support. Recent studies show how the growth hormone produced during pregnancy increases nitrogen retention in the tissues in the form of protein.[7] It aids nitrogen conservation whenever dietary protein and carbohydrate are in short supply. This hormone or its companions influence fatty acid and ketone body metabolism.[8] Pregnancy increases vitamin B_{12} absorption.[9] Parathyroid hormones have been shown to act as biological regulators of calcium metabolism.

Blood Volume Increases.—There is an increase in plasma volume during pregnancy that averages approximately 25% at term over the nonpregnant

value. A sharp increase occurs through the second trimester and during the first half of the third trimester, after which the plasma volume tends to remain constant or to decrease. In evaluating results of blood studies during pregnancy, a major physiological influence is known to be the change in blood volume.[10]

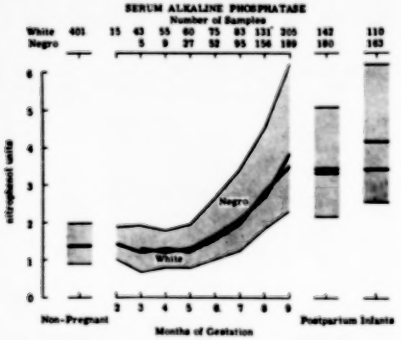
SERUM ALKALINE PHOSPHATASE
Number of Samples
White 401 15 43 56 60 75 83 131 205 142 110
Negro 5 9 27 52 95 156 189 180 143
Negro
White
Non-Pregnant
Months of Gestation
Postpartum Infants

Fig. 5.—Trend of median serum alkaline phosphatase levels of white nonpregnant women, of selected white and Negro women during gestation and after delivery, and of their respective newborn, term infants. The 10th-90th percentile range for combined racial groups serves as standard for normality.

Biochemical Changes

During pregnancy many biological changes occur. The liver, kidneys, adrenals, and other vital organs develop functional activity commensurate with the stage and demand of gestation. Single determinations contribute little to the evaluation of biochemical individuality and customary responses; however, successive determinations performed as metabolic and physiological functional changes are taking place show individual patterns and deviation from established patterns.

Blood Determinations.—Any interpretation of physiological trends during gravidity, however, must recognize alterations in blood volume, since blood volume increases. If there are no changes in the concentration of the blood constituents with pregnancy, it is obvious that there are increased amounts in the bodies of mother and fetus. An increase in concentration indicates an even greater increase in the supply available.

Until methods for determining blood volume become easier to administer to groups of individuals, we have assumed that, if differences in gestational weight changes are not appreciable among healthy female subjects, the blood volume changes are similarly not significant. This assumption is necessary for comparisons of the cencentrations of several blood components from the various groups at equivalent stages of gestation. In our studies, the characterization of the various groups suggests that, in the interpretation of the data on the basis of nutritional status, investigations of racial characteristics, of inequality of nutrient intake, and of prenatal care should also be undertaken.

We have presented observations [11] made on selected subjects who successfully completed gestation and delivery without any unusual disturbance or disease and who were delivered of healthy, full-term infants weighing at least 2,500 Gm. (5.5 lb.). Criteria for selection included consideration of medical history, clinical course during pregnancy, and outcome of gestation, with respect to both mother and child. Excluded from the group were women with physical structural defects, congenital or acquired, and those in whom malnutriture or disease had left recognizable clinical effects so serious that their health might have been permanently impaired. If either mother or infant were to be omitted for any of these reasons, both were excluded. Such conditions as syphilis and toxemia during current pregnancy were bases for categorical exclusion from the selected group. In some instances, obstetric judgment combined with pediatric consultations in relation to the condition of the infant were determining factors. Women whose deliveries involved operative procedures were excluded as well as those who were in labor over 24 hours. The blood values for 48 nonpregnant white women provided a basis for observing the physiological alteration from the nonpregnant to the pregnant state; those

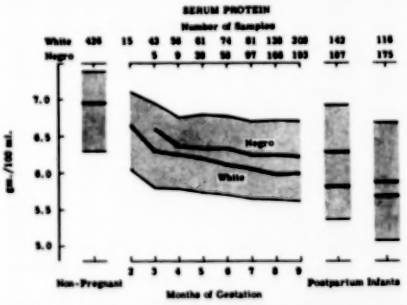

Fig. 6.—Trend of median serum protein levels of white nonpregnant women, of selected white and Negro women during gestation and after delivery, and of their respective newborn, term infants. The 10th-90th percentile range for combined racial groups serves as standard for normality.

values for the selected group of 425 patients, chosen because they were free from clinical manifestation of disease, provided average and range values that may be used as standards for departures from health.

In obtaining data for blood composition, unaccountably high or low results may occur which may not be true values. Such figures were eliminated by including values in the 10th to 90th percentiles, which characterize the usual physiological course during pregnancy. The medians and the 10th to 90th percentile ranges for hemoglobin, serums total protein, vitamin A, carotenoids, vitamin C, and alkaline phosphatase are presented. Data are also given for nonpregnant women, for the selected white and Negro women during pregnancy and for one to eight days post partum, and for their full-term infants one to nine days after birth.

Hemoglobin.—The medians and ranges for hemoglobin throughout pregnancy were lower than those of the nonpregnant women (fig. 1). The range of levels for white women was higher than the range for Negro women, indicating a difference in the racial groups. The median hemoglobin values for women of the white race were 0.7 to 1 Gm. higher than those for women of the Negro race during the last months of pregnancy. Selected white infants displayed hemoglobin levels higher by as much as 1 Gm., and the median levels were approximately 50% greater than the values of their respective mothers.

The extent to which hemoglobin will be formed depends, in large measure, on the availability in the body of iron and organic components for porphyrin formation and of essential amino acids for globulin formation. The number of organs and components in the body and the food components that converge to help perfect the synthesis, the metabolism, the distribution, and the destruction of hemoglobin are legion. The mechanisms that control the distribution of essential amino acids are little understood. Normally, the fetus acquires a reserve store of iron from the maternal organism via the placenta, especially during the last trimester of pregnancy. The placenta appears to conserve hemoglobin for fetal construction and reserves at the expense of the mother. An overstrain on the function of hematogenesis is shown by the mild secondary anemia, common in pregnancy. The physiological anemia (normocytic) of pregnancy is due to dilution by blood volume increase and causes no radical change in the alteration of the blood picture, since the reduction in hemoglobin, erythrocytes, and hematocrit is in direct proportion. To what extent particular hormonal factors in pregnancy alter the rate of the blood-building process and the development of an anemic state in pregnancy is being investigated.[12]

Serum Ascorbic Acid.—The serum of nonpregnant white women had higher concentrations of ascorbic acid than that of the selected white women in the first trimester of pregnancy (fig. 2). A downward trend throughout pregnancy extended into the postpartum period, but throughout gestation the levels of the white women were much higher than those of the Negro women. The ascorbic acid levels of the Negro women, though much lower earlier in pregnancy, did not show as much decline before delivery. The ascorbic acid concentrations in infant blood were almost alike for the two races, but the range was higher for white infants.

A shortage of ascorbic acid in the diet during pregnancy may thwart the growth impulses of the mother and her offspring in utero by impairing physiological function. Average serum concentrations of this vitamin for infants are two to four times that of the mothers' serum. This fact gives credence to the theory that the placenta exerts selective control over the passage of ascorbic acid and may act as a barrier to re-entrance of the vitamin into the maternal circulation.

Without doubt, endocrine changes exert some influence on maternal blood levels of ascorbic acid, just as the ascorbic acid content of the adrenal gland is high in pregnancy. Ascorbic acid and proteins are involved in the metabolic mechanism of the adaptation syndrome occurring during the stress of physiological disturbances in pregnancy. It is generally recognized that fetal needs take priority over maternal needs for this vitamin and that the fetus may build up a substantial reserve of it at the expense of the mother.

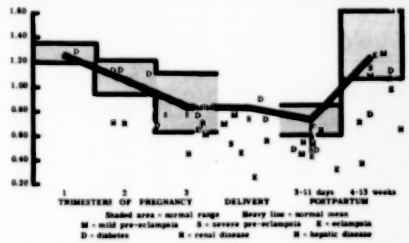

Fig. 7.—Albumin:globulin ratio in maternal blood during and after pregnancy.

Serum Vitamin A.—The median concentrations of serum vitamin A of nonpregnant white women and selected white patients in the first trimester were not different (fig. 3). The median values were consistently higher for white than for Negro women during the last five months of gestation and post partum. Although the difference between the medians for white and Negro infants was small, that of the Negro was lower. Vitamin A and its precursors, the carotenoids, have special roles in the formation of the epithelial cells during organogenesis, in the maintenance of their integrity, and in the formation of bone.[13]

Serum Carotenoids.—The median serum carotenoid level for nonpregnant white women was higher than that for the selected white subjects in the first

trimester (fig. 4). For both white and Negro subjects, however, upward trends in early pregnancy were followed by leveling off after the sixth month and lowered values post partum. The levels for white and Negro infants were not different but were much lower than those of their mothers.

Serum Alkaline Phosphatase.—The pattern for serum alkaline phosphatase is different from those for hemoglobin and the vitamins, because its concentration in serum more directly parallels skeletal growth and maturation in the fetus and mineral storage in the maternal organism. The trend was definitely upward through the ninth month, with the levels decreasing in the puerperium (fig. 5).

Alkaline phosphatase enzymes are widely distributed in the organs and tissues of the body, occurring in high concentration in bone and ossifying cartilage. Their activity is related to calcium homeostasis [14] and vitamin D nutriture. Data demonstrate that physiological changes in alkaline phosphatase concentration occur with regularity during the reproductive cycle, the magnitude of change corresponding in large measure to anatomic growth and development.

Blood Proteins.—Levels of total serum protein of nonpregnant white women were higher than medians for white and Negro women at any time during gestation (fig. 6). For women of both races, the trend of serum protein concentrations was downward throughout pregnancy, the median differences ranging from 0.11 to 0.46 Gm. per 100 ml. of serum. The protein levels of infants were lower than those of their respective mothers, and both the median and the range for the Negroes exceeded those of the white race.

The intensity with which the maternal body builds active body tissue, the rapidity with which labile protein and mineral reserves are accumulated, and the extent of alterations taking place in hormonal excretions may influence the level of serum protein. Physiologically, total serum protein has less significance than the quantities and properties of the several component proteins, each one differing in composition and performing widely different physiological functions in the body.

Observations of levels of total serum protein, albumin, and alpha$_1$, alpha$_2$, beta, phi, and gamma globulins during pregnancy and subsequent to delivery demonstrated a characteristic pattern of distribution of these components for uncomplicated pregnancy; the pattern is disturbed in complicated pregnancy,[15] however, and some diseases present distinctive patterns (fig. 7).

Electrophoretic analysis of the proteins in plasma or serum provides a more detailed and reliable picture of this labile biological system than do other methods, although values are frequently lower than those obtained by chemical methods. Data for women during and after both uncomplicated and complicated pregnancies demonstrated the variations attributable to individual physiological differences among women, as well as differences in the time of the cycle during which the blood samples were drawn. In general, trends for albumin and gamma globulin were downward; trends for alpha$_1$, alpha$_2$, beta, and phi (fibrinogen) globulins were upward until delivery or at term; subsequently, the trends were reversed and the values approached those of the nonpregnant state. The plasma albumin: globulin ratios for each period in the reproductive cycle showed the decreases consequent to lowered albumin concentration and higher globulin concentration during pregnancy, with the return post partum toward the nonpregnant relationship. During the first trimester (preimplantation and organogenesis phases), the decreases in albumin

*Proteins in Blood Plasma of Mothers During Pregnancy, at Delivery, and Post Partum**

	Trimester of Pregnancy†			Delivery	Post Partum		
Determinations	1 3	2 7	3 15‡	16	12-24 Hr. 3	5-6 Days 9	6-12 Weeks 13
Albumin							
Mean	4.22	3.89	3.43	3.41	2.68	3.15	4.07
Range	3.79-4.62	3.37-4.41	2.43-4.07	2.51-4.60	2.45-2.91	2.78-3.58	3.40-4.71
Alpha$_1$ globulin							
Mean	0.40	0.44	0.51	0.48	0.54	0.69	0.42
Range	0.32-0.45	0.34-0.58	0.32-0.72	0.40-0.60	0.43-0.66	0.59-0.77	0.33-0.51
Alpha$_2$ globulin							
Mean	0.70	0.77	0.87	0.94	0.86	1.10	0.66
Range	0.67-0.76	0.65-1.00	0.66-1.15	0.46-1.32	0.58-1.10	0.71-1.29	0.58-0.89
Beta globulin							
Mean	0.96	1.20	1.36	1.40	1.22	1.38	1.05
Range	0.90-1.04	0.92-1.48	0.94-1.95	1.11-1.83	1.17-1.29	1.17-1.57	0.83-1.29
Phi globulin							
Mean	0.55	0.58	0.65	0.70	0.67	0.69	0.43
Range	0.51-0.57	0.49-0.73	0.50-0.92	0.45-1.07	0.61-0.76	0.54-0.90	0.28-0.65
Gamma globulin							
Mean	0.73	0.69	0.68	0.62	0.50	0.54	0.78
Range	0.64-0.87	0.56-0.83	0.46-0.93	0.32-0.87	0.44-0.56	0.27-0.64	0.57-1.15
Total protein							
Mean	7.06	7.37	7.50	7.55	6.47	7.55	7.41
Range	6.88-8.06	6.37-8.70	5.96-8.68	5.86-10.36	5.93-7.23	6.67-8.48	6.20-8.20

* Values in Gm./100 cc. of plasma.

† According to estimated date of confinement, determinations in first trimester were made in 4th to 9th week of pregnancy; those in second trimester were made between 15 and 25 weeks of gestation; those in third trimester were made after 28 to 41 weeks of pregnancy.

‡ Fourteen subjects. In all other groups, number of determinations also is number of subjects.

and gamma globulin were obvious; in the second and third trimesters (growth phase), the concentrations of albumin and gamma globulin in total protein were reduced significantly.

Summary

Pregnancy causes the regulatory and functional mechanisms of the body to be thrown out of balance. The effects of these imbalances are frequently seen as upsets in the gastrointestinal system. Results of the metabolic changes are observed in the composition of the blood cells and in the differing levels and distribution of the blood components. The levels of urinary components, the changes in hormonal secretions, the greater retention of nutrients, and the composition and function of the placenta are all indications of the metabolic changes that take place at the time of or after conception.

Figures 1 through 6 are reproduced with permission from Macy and others.[11]

The table and figure 7 are reproduced with permission from Macy and Mack.[16]

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NEW ANATOMICAL NOMENCLATURE.—An International Anatomical Nomenclature Committee was set up, and the work of this Committee resulted in the Paris Nomina Anatomica of 1955. . . . Major changes are few. One or two structures familiar in clinical practice, are however, affected. The circumflex nerve, for example, is now the axillary nerve, even though it quickly leaves the axilla and though its accompanying artery is still called the posterior humeral circumflex artery. The internal mammary artery becomes the internal thoracic artery. The accessory nerve, which has always been a little troublesome, is now described as having an internal branch (cranial part), and an external branch (spinal part). The moderator band of the right ventricle is to be known officially as the trabecula septomarginalis, and certain details of the heart valves are changed. . . . At present, in British textbooks, it is usual to name the cusps of the pulmonary valve posterior, right, and left; in the new list they are given as anterior, right, and left. Similarly the cusps of the aortic valve have been changed from anterior, right, and left to posterior, right and left. . . . A name has now been found for the "Artery Without a Name." One has often wondered why a vessel which supplies one-eighth, let us say, of the body with blood should have been called the innominate artery, or, what sounds even more casual to English ears, the B. A. (1895) term—Arteria Anonyma. Now it is to be called the brachio-cephalic trunk—not an elegant name perhaps, but at any rate, "nomen proprium," a name of its own.—R. M. Livingstone, The New Anatomical Nomenclature, *Annals of the Royal College of Surgeons of England*, May, 1958.

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HISTOPLASMOSIS

HISTOPLASMOSIS was first described in 1906 and until about 1940 it was considered to be an acute, progressive, almost invariably fatal disease. It is now recognized that in addition to the progressive disseminated type there is a much commoner type that is benign, self-limited, and often asymptomatic.[1] According to Tegeris and Smith [2] the case fatality rate in epidemics is about 1.2%. The distribution seems to be world-wide but the disease is more prevalent in rural than in urban areas and in some rural regions than in others.[3] The causative fungus, Histoplasma capsulatum, is found in the feces of birds (especially domestic fowl), bats, dogs, and various other mammals, hence it is commonly found in the soil.

Primary infection with the development of a single tuberculoid nodule in the lung is almost always of the benign type but, if there is an overwhelming exposure to contaminated dust, multiple pulmonary lesions may result from hematogenous spread. In older patients about 50% develop cutaneous or mucocutaneous lesions (nodules, papules, ulcers, abscesses, and furuncles). The spleen may be enlarged. The patient may have a cough which is usually unproductive, chest pains of varying intensity, loss of weight, increased fatigability, and general malaise. The condition usually is first suggested when the characteristic changes are seen in a roentgenogram of the chest. As in the case of tuberculosis, a positive skin test indicates previous contact with the causative organism but gives no information regarding activity. The complement-fixation test is the only serologic test that is of much value as an index of activity, but it is so complex that it is done only in a few special laboratories.[1]

The diagnosis is difficult because neither the clinical nor the x-ray findings are pathognomonic and the disease simulates many other conditions. In endemic areas histoplasmosis in white children up to age 18 is at least eight times as common as tuberculosis.[4] Many patients with pulmonary cavities due to histoplasmosis are still admitted to tuberculosis hospitals despite the absence of any positive evidence of tuberculosis. This is unfortunate because streptomycin (and also penicillin) is contraindicated in the treatment of histoplasmosis as it favors the growth of the organisms.

The benign type of this disease requires no treatment. In the effort to find an effective treatment for the progressive type many drugs have been tried and sometimes the results reported by one observer differ radically from those reported by another. Christie [3] used sulfonamides with good results even in patients with progressive lesions. For this reason he believes these drugs may be lifesaving. The response of the patients was not apparent for a week or two but within three or four weeks the patients were well and no relapses were observed. The most controversial drug is amphotericin B. Lehan and co-workers [5] found it relatively nontoxic and suggested that it might have some therapeutic usefulness. Later they reported improvement in patients with the progressive type of lesion when the drug was given by mouth but relapse when it was discontinued. Two patients given the drug intravenously showed marked clinical and bacteriological improvement but two others with far-advanced lesions treated in this way died. Christie stated that although some favorable results with this drug have been reported it is likely to produce chills and fever and may cause renal damage. Packard and co-workers [6] used cortisone and believed that the drug probably shortened the course of the disease and saved life but reserved its use until after two weeks of illness had elapsed. This allowed the body to develop an immune reaction. Immediate use of this drug might further the spread of the disease and suppress antibody formation.

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THE PRESIDENT'S PAGE

A MONTHLY MESSAGE

Additional positive steps were taken by the House of Delegates at the recent A. M. A. Clinical Meeting in Minneapolis for meeting the medical care needs of the indigent. It is my personal wish that all physicians will participate with their state and county medical societies in developing the best possible programs for public assistance recipients.

Currently there are a multiplicity of programs for medical care of the indigent under the Social Security Act. According to the law, each state must keep its programs for (1) old-age assistance, (2) aid to dependent children, (3) aid to the permanently and totally disabled, and (4) aid to the blind administratively and financially distinct. This separation leads to confusion, waste, and duplication.

To help correct this situation the Council on Medical Service recommended and the House of Delegates approved a resolution that the Social Security Act be amended by Congress to permit states to combine the present four public assistance medical programs into a single medical program, administered by a single agency and making available uniformity of services to all eligible public assistance recipients in the state.

Regarding the program administration by a single agency, the House concurred in the recommendation that each state medical association give serious consideration to the use of a "voluntary agency such as Blue Shield" or a "specific agency established by the medical society" for administering any funds provided under the public assistance provisions of the Social Security Act for medical care of the indigent.

Some state associations already use such administrative agencies, and I urge others to experiment with the use of similar mechanisms.

Because the medical profession has accepted the principle that the provision of personal health services to the needy is primarily the responsibility of the state and local governments, it now is our duty to see that the best possible programs are developed and administered at these governmental levels.

In communities where physicians prefer to provide care through their own charity, rather than being paid from welfare funds, I sincerely hope that definite programs will be established to assure that every needy person has the necessary physician's services to the extent available in the community.

Furthermore, I agree with the Council on Medical Service and the House that "medical societies establish formal liaison with governmental agencies concerned in the provision of health services to the indigent in their areas, and through such liaison they act in an advisory capacity to assure the adequacy of the health care of those who cannot meet the cost of such care through their own resources."

Finally, I believe that in some areas nonindigent and nondeserving persons now have access to public assistance services. Therefore, I concur with the Council and the House that indigent care committees must inform themselves regarding laws and regulations governing determination of eligibility and must examine both the validity of these standards and their application.

By its actions on the Council's recommendations the House has laid the foundation for a strong, medically sponsored program to implement existing policy statements concerning personal health services to the needy. It also has outlined a positive program of local action which will serve as a bulwark against further federal entry into the field of medical care. Let us provide the active and organized support needed to make the program a reality in every state and community.

GUNNAR GUNDERSEN, M.D.
La Crosse, Wis.

SCENES FROM THE MINNEAPOLIS MEETING

Left, A. M. A. House of Delegates during 12th Clinical Meeting in Minneapolis, Dec. 2-5, 1958.

Above, Reference Committee on Insurance and Medical Service meets to discuss resolutions introduced to House of Delegates.

Left, Dr. Gunnar Gundersen, La Crosse, Wis., A. M. A. President, addresses House of Delegates.

One of the many preconvention meetings was the Conference on Federal Medical Services.

General Practitioner of the Year, Dr. Lonnie Coffin of Farmington, Iowa, is welcomed to House of Delegates by Dr. E. Vincent Askey, House Speaker, and Dr. Louis M. Orr, A. M. A. President-elect.

Above, Dr. Charles V. Heck *(left)*, University of Illinois College of Medicine, and Dr. Harry B. Hall, University of Minnesota Medical School, present Auditorium exhibit featuring fractures encountered by front seat passenger in auto crash.

Left, Dr. J. T. Lowe, Indianapolis, receives a copy of A. M. A.'s new pamphlet, "The Healthy Way to Weigh Less," being distributed at Council on Foods and Nutrition exhibit on weight reduction. Pamphlet will be mailed to all medical societies later this month.

Right, Dr. Peter A. Salmon demonstrates his work with massive hemorrhage by local gastric hypothermia with wax models and a hypothermia machine. Dr. Edward W. Kieffer *(left)*, Elmore, Ohio, was one of many physicians to study his work.

Chemotherapeutic application of isolated organ perfusion is outlined to Dr. Howard M. Frykman *(left)* of Minneapolis by exhibitors Dr. R. K. Ausman and medical technologist Sharon Semmill of the University of Minnesota.

Twin coil artificial kidney is explained by Dr. John F. Maher, Georgetown University School of Medicine, to Dr. Joseph Rosenfeld *(right)* of Philadelphia.

Right, Tom Gardiner, rounding out 50 years of service on A. M. A. staff, attends his last Clinical Meeting before retiring Jan. 1. He checks operational schedule of meeting with his secretary for 16 years, Miss Rita Huster, in the Auditorium.

Above, Tom Creagh of Chicago was an early bird in setting up demonstration of cold steam humidifier in Industrial Exhibition.

Right, Dr. Herman Kleinman, in "Indian Medicine in Minnesota" exhibit in Auditorium, is awarded feathered finery for his work on Redlake Indian Reservation.

Seated as representatives of Student American Medical Association are Marvin J. Chapman *(left)*, University of Wisconsin Medical School, and William Kirkham, University of Oklahoma Medical School. They are S. A. M. A. regional vice-president and treasurer respectively.

Mrs. Arthur E. Underwood of Vancouver, Wash., President of Woman's Auxiliary to A. M. A., addresses House of Delegates.

MEDICAL NEWS

ARKANSAS

County Society Aid for Research Laboratory.—The Pulaski County Medical Society gave $10,187 to the University of Arkansas Medical Center, Little Rock, Oct. 17 to establish a Virus Research Laboratory in the proposed new 2-million-dollar Research Wing to be built at the center. The check was presented to Dr. F. Douglas Lawrason, provost for medical affairs, by Dr. Hoyt Choate, society president, and Dr. Jerome S. Levy, chairman of the society's Committee for Distribution of Surplus Funds. The money will be matched by federal funds in the construction of the Research Wing. The government has allocated $1,066,000 to the university. Dr. Choate said the reserve money had been building up in the society's funds for a number of years. Out of a large number of possible uses that were considered, it was decided unanimously by the committee that it could best be utilized at the Medical Center.

CALIFORNIA

New Deadline for Heart Research Funds.—A new deadline—Feb. 1, 1959—has been established for applications for research funds from the Los Angeles County Heart Association. The deadline formerly was April 15. Decision to advance the final date for applications was announced by Dr. Mitchel D. Covel, chairman of the Research Committee. Dr. Covel said the earlier deadline is to the advantage of local investigators because their applications can be distributed by the California Heart Association through the state and in turn attract additional funds to local investigators from other chapters. As changes have been made in application methods, investigators are advised to contact the Heart Association at 660 S. Western Ave., Los Angeles, DUnkirk 5-4231, for a copy of the New Application Information bulletin. Under the new schedule, applications will be referred to study sections of the committee by Feb. 10. Final notification of awards will be made on June 1 and projects will be funded on July 1.

DISTRICT OF COLUMBIA

Campaign for Hospital Research Center.—Children's Hospital of the District of Columbia has launched a campaign to raise $460,000 to complete its new Research Center and finance other improvements to the hospital at a total cost of $1,117,357. Grants totaling $457,357 and a $200,000 pledge from the Variety Club of Washington, D. C., were received before the campaign opened. The Research Center is now under construction at Twelfth and W. Sts., N.W. Scheduled for completion in January, 1959, the building will cost about $800,000. The three-story structure will provide facilities for research in allergy, antibiotics, adolescent medicine, cystic fibrosis, hematology, psychiatry, renal diseases, and viral diseases. Movable partitions will allow rearrangement of research areas without extensive repairs. Research is currently conducted in scattered laboratories within the hospital. New parking facilities, air conditioning, an expended medical library, a psychiatric center, and a recovery room are among the other projects to be financed by campaign funds.

FLORIDA

Study of Caribbean Tropical Disease.—Twelve University of Miami graduate students in medicine and zoology will study tropical diseases and parasitology in Central America and the Caribbean as a result of a $19,000 educational grant received by the university from the National Institutes of Health, Washington, D. C. J. Walter Beck, Ph.D., associate professor of microbiology, will accompany six medical students to Costa Rica for a month's study of parasites and tropical disease. W. Henry Leigh, Ph.D., professor of zoology, and Dr. Ralph Jones Jr., chairman of the department of medicine, will supervise the training program. Another group of six graduate physicians who are residents specializing in internal medicine will undertake similar studies in Jamaica. In Costa Rica, the San Juan de Dios Hospital of San Jose will be headquarters while in Jamaica the training program will stem from the British Medical College of the West Indies.

HAWAII

Colonel Hughes Receives Award.—The Wellcome Prize was awarded to Lieut. Col. Carl W. Hughes, M. C., U. S. Army, Nov. 19, at the 65th annual convention of the Association of Military Surgeons of the United States. Colonel Hughes, a native of Missouri, is chief of general surgery service at Tripler Army Hospital in Honolulu. The Wellcome Prize is presented annually at the discretion of the association for "the best essay on medico-military affairs prepared by one of its members." The prize consists of a silver medal, a scroll, and an honorarium of $500. The Wellcome Prize essay for 1958 is entitled "Vascular Surgery in the Armed Forces."

Physicians are invited to send to this department items of news of general interest, for example, those relating to society activities, new hospitals, education, and public health. Programs should be received at least three weeks before the date of meeting.

MASSACHUSETTS

Workshop on Instrumentation.—A five-day Instrumentation Workshop will be held April 13-17, 1959, at Harvard Medical School, Boston, under the auspices of the Clinical Pathology Committee of the New England Society of Pathologists. The workshop covers actual participation in:

1. Use of Beckman DU spectrophotometer and
2. pH meters
3. Assembling ammeter-voltmeter for your own use
4. Trouble shooting on photometers
5. Studying blood pH methodology
6. Constructing spectral absorption curves in visible and ultraviolet
7. Photofluorimetry
8. Practical program of laboratory maintenance.

Registration should be made immediately.

MICHIGAN

Distinguished Citizen's Award.—The Dearborn Chamber of Commerce has announced that Dr. Sidney E. Chapin won its "Distinguished Citizen's Award" for 1958. The presentation was made Oct. 28. Dr. Chapin is secretary of the Michigan Heart Association, is chairman of both the Health Federation, United Community Services of Detroit, and Public Relations Committee of the Wayne County Medical Society, has served as chairman of Dearborn Public Health Committee and the Steering Committee of Child Guidance Project West Wayne County, and is the vice-president of Detroit Men's Council Navy League of the U. S.

MISSOURI

Name Chairman of Nutrition Committee.—Dr. Robert L. Jackson, chairman, department of pediatrics, University of Missouri School of Medicine, Columbia, has been appointed chairman of the Committee on Infant Nutrition by the Food and Nutrition Board of the National Research Council, Washington, D. C. The Committee on Infant Nutrition has the responsibility of accumulating and interpreting scientific data on infant nutrition, defining the unsolved problems, and pointing out areas for future research. It also advises the National Research Council on revision of recommended dietary allowances. Establishment of the committee was authorized by the Food and Nutrition Board last spring. Other members of the committee are Dr. Harry H. Gordon, Baltimore; Dr. Paul Gyorgy, Philadelphia; Wendell H. Griffith, Ph.D., Los Angeles; Dr. Charles U. Lowe, Buffalo, N. Y.; and Dr. Joseph A. Johnston, Detroit.

NEBRASKA

Psychiatric Institute Wins Award.—The Nebraska Psychiatric Institute received the 1959 Mental Hospitals Achievement Award of the American Psychiatric Association. The association's silver plaque was conferred on the Omaha institution "in recognition of its leadership in creating a statewide mental health program." The award was presented at the 10th Mental Hospital Institute by Dr. Mathew Ross, medical director of the American Psychiatric Association, to Dr. Cecil Wittson, director of the institute. The citation read: "Nebraska's decision to invest in a psychiatric research and training facility, rather than just adding more hospital beds, has paid dividends in a dynamic program that has benefited the entire state and aids the Dakotas and Iowa." Community clinics and orientation courses for clergymen, teachers, and general practitioners aided in the program. Nebraska has pioneered in the use of an interstate telecommunication system and closed-circuit television for training in psychiatric centers.

NEW YORK

Dr. Wagner Named Executive Director.—Dr. Herbert T. Wagner, Bronxville, became the new executive director of the Medical Society of the State of New York Dec. 1, it was announced by Dr. Leo E. Gibson, Syracuse, president of the society whose headquarters are at 750 Third Ave., New York City. Dr. Wagner will take over the management of the society's staff of 70 employees who work in the membership and directory departments, the Bureau of Industrial Health and Workmen's Compensation, the Bureau of Medical Care Insurance, and the Bureau of Public and Professional Relations. The society, which last year celebrated its 150th anniversary, also publishes the *New York State Journal of Medicine*. Dr. Walter P. Anderton, secretary of the society for many years, who formerly had the dual position of secretary-general manager, will continue as the society's elected secretary.

Establish Institute for Rheumatic Fever.—New York University and Irvington House have agreed to establish the Irvington House Institute for Rheumatic Fever and Allied Diseases as a part of New York University–Bellevue Medical Center. The institute will be housed in the new University Hospital. Irvington House will underwrite the cost of $500,000 toward the construction of the treatment, research, and clinical facilities. Both Irvington House and the Medical Center have been responsible for original research on rheumatic fever. Irvington House, at Irvington-on-Hudson, is a hospital and research center for children afflicted with diseases of the heart. Since its beginning in 1920, it has cared for over 5,800 children. The university and Irvington House, while joining in the creation and operation of the institute, will continue to function as autonomous, financially independent institutions. New York University–Bellevue Medical Center will appoint the central committee of

the institute, to function as a communications center for the research programs in rheumatic fever and those allied diseases which are initiated by streptococcal infection. Members of the Irvington House Medical Advisory Committee will be nominated by the university and elected by the Irvington House board.

New York City

Hospital News.—A $350,000 project involving the installation of a postoperative recovery unit and expansion of the operating theatre and the x-ray department has been completed by The Bronx Hospital, Dr. Aaron A. Karan, hospital director, has announced. The three facilities are housed on the eighth floor of the main building. A $172,000 grant from the Ford Foundation paid for half the cost of the project. The other 50% expense was met by the Federation of Jewish Philanthropies and the hospital's own building fund resources.

NORTH CAROLINA

Dr. Warren Goes to Texas.—Dr. James V. Warren, professor of medicine at the Duke University Medical Center, Durham, has left to become chairman, department of internal medicine, University of Texas Medical School, Galveston. A Duke faculty member since 1952, Dr. Warren is known for his research on heart disease. Two years ago he visited Africa as a member of an international team which made a blood pressure study of giraffes, a project conducted under a contract between Duke and the U. S. Office of Naval Research to provide data related to the problem of blackouts among high-speed aircraft pilots. Dr. Warren served in 1952 as president of the American Federation for Clinical Research. He is a member of the editorial boards of the "*American Heart Journal*," "*Heart Bulletin*," and the cardiovascular section of "*Excerpta Medica*."

PENNSYLVANIA

Philadelphia

Dedicate Quarters for New School.—The School of Allied Medical Professions of the University of Pennsylvania dedicated its new quarters at 39th and Pine Streets, Philadelphia, Nov. 25. The building is a completely renovated former convent. Following a tour by 90 guests representing local, state, and national health, rehabilitation, and educational agencies, Basil O'Connor, president of the National Foundation, spoke on "Careers that Count." The building makes it possible for various programs of the School of Allied Medical Professions to be housed under one roof. These programs include physical therapy, occupational therapy, medical technology, and oral hygiene. Administrative and instructional activities of the school were moved into the new quarters Sept. 1.

Dr. Hodes Named to Head Radiology Department.—The Board of Trustees of Jefferson Medical College has appointed Dr. Philip J. Hodes as professor and head of the department of radiology and as attending radiologist of Jefferson Hospital succeeding Dr. Russell L. Nichols. Dr. Hodes has been professor of radiology at the Medical School and at the Graduate School of Medicine, University of Pennsylvania since 1952. He has also been associate in radiology at the hospital of the University of Pennsylvania since 1955. In Philadelphia he is consultant for the U. S. Naval Hospital, The Veterans Administration Hospital, and Jeanne's Hospital; and in Washington, Walter Reed Army Hospital, and the Armed Forces Institute of Pathology. He is a diplomate of the American Board of Radiology and a past-president of the Philadelphia Roentgen Ray Society.

Begin Construction on Research Building.—The University of Pennsylvania School of Medicine has begun construction on its new Research Building, a $3,100,000 structure, to be devoted solely to medical science research. An additional building is planned for the department of biology and is to be located adjacent to the Medical Research Building. Classrooms, libraries, and offices of the School of Medicine Building, laboratories of the Medical Research Building, and the college's departments of biology and zoology will all be interconnected. The research building itself will be characterized by four seven-story towers connected by a common, central section. When completed the building will be occupied by the departments of microbiology and physiology, the Phipps Institute section of the department of public health and preventive medicine, the Harrison department of surgical research, and the Johnson Foundation for biophysical research. It is being financed by the university and the U. S. Public Health Service under the Federal Research Facilities Act. The University's contribution of $1,600,000 will be matched by a Public Health Service grant of $1,500,000.

GENERAL

Survey of Research in Tropical Medicine.—A survey to determine the adequacy of research and training in tropical medicine in the United States will be undertaken by the National Research Council, Washington, D. C., with financial support from the National Institutes of Health, the Department of Defense, and The Rockefeller Foundation. The foundation is contributing $26,000 over a three-year period. The survey will seek information on the status of tropical diseases which affect human beings and animals and are of economic importance, and will evaluate the research and development work now in progress. A special staff appointed by the National Research Council will conduct the study and formulate recommendations.

Award for Cancer Research.—The Ann Langer Cancer Research Foundation has announced an annual award of $500 for meritorious investigation in the field of cancer research, either clinical or laboratory. The award is being supported by the family of the late Bertha Goldblatt Teplitz. Competition shall be limited to physicians and other scientists under the age of 45. The Award Committee consists of Drs. Austin M. Brues, Israel Davidsohn, Danely P. Slaughter, Albert Tannenbaum, and William B. Wartman, of Chicago. Nominations should be submitted to Tiplitz Award Committee, 612 N. Michigan Ave., Chicago 11 by Feb. 1, 1959, and should be accompanied by a short one-page statement and biography.

Plans for New Library of Medicine.—Preliminary plans for the new building of the National Library of Medicine have been submitted to the Public Buildings Service, the Public Health Service has announced. The new building will be constructed on the grounds of the National Institutes of Health in Bethesda, Md. Plans call for 232,000 square feet of space, on five levels, three of which will be below ground level. The 85th Congress appropriated 7 million dollars for construction, which will begin in spring, and the building is expected to be completed in 1961, the 125th anniversary of the library's founding. The National Library of Medicine, operated by the Public Health Service of the Department of Health, Education, and Welfare, is reportedly the largest medical library in the world.

Prize for Medico-Surgical Film.—The "Annual Prize for Medico-Surgical Cinema," which comprises 100,000 francs cash (with possibility of being divided) and various other awards, will be given during the last session of the course of "Actualities Medico-Chirurgicales" at the "Nouvelle Faculte de Medicine de Paris" March 17, 1959. The didactic value of the film as well as its properly cinegraphic quality will be considered. Only the 16 mm. size film will be admitted. Candidatures and films are to be sent to the "Secretariat du Journal La Presse Medicale," 120 Boulevard Saint Germain, Paris VI°, prior to Feb. 15, 1959. Awards will be remitted to the authors of the best films. Contrary to the preceding years, all the films may be given awards, including those subsidized or produced by a laboratory or firm.

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Award for Cancer Research.—The Ann Langer Cancer Research Foundation has announced an annual award of $500 for meritorious investigation in the field of cancer research, either clinical or laboratory. The award is being supported by the family of the late Bertha Goldblatt Teplitz. Competition shall be limited to physicians and other scientists under the age of 45. The Award Committee consists of Drs. Austin M. Brues, Israel Davidsohn, Danely P. Slaughter, Albert Tannenbaum, and William B. Wartman, of Chicago. Nominations should be submitted to Tiplitz Award Committee, 612 N. Michigan Ave., Chicago 11 by Feb. 1, 1959, and should be accompanied by a short one-page statement and biography.

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Hoffmann, Detroit; vice-president, Dr. Oscar B. Markey, Cleveland; and secretary-treasurer, Dr. Ralph M. Patterson, Columbus, Ohio. The next meeting will be held in New Orleans, Oct. 16-17, 1959.——The following officers were elected at the recent meeting of the **North Central Medical Conference** Oct. 11-12: Dr. Lien O. Simenstad, Osceola, Wis., president-elect for the year 1960; secretary, Mr. Harold W. Brunn, who will become executive secretary of the Minnesota State Medical Association Jan. 1, 1959; secretary-emeritus, R. R. Rosell, who is now executive secretary of the Minnesota State Medical Association and who will retire Dec. 31. President-elect for 1959 is Dr. Arthur J. Offerman, Omaha.——At the interim meeting of the **American Institute of Ultrasonics in Medicine** held Aug. 23 Dr. Jerome W. Gersten, Denver, was elected president and Dr. John H. Aldes, Los Angeles, was elected secretary-treasurer.——Dr. William S. Kroger, clinical associate professor of obstetrics and gynecology, Chicago Medical School, was elected president of the **Academy of Psychosomatic Medicine** at its recent annual meeting in New York City. Other officers are: Dr. Maury D. Sanger, Brooklyn, vice-president; Dr. Bertram B. Moss, Chicago, secretary; Dr. Zale A. Yanof, Toledo, Ohio, treasurer; and Dr. Morris M. Peshkin, New York City, historian. Dr. Wilfred Dorfman, of Brooklyn, as president-elect, will succeed to the presidency at the sixth annual meeting of the academy next October at Cleveland.—— Dr. James C. Overall, of Nashville, Tenn., has been elected president of the **American Academy of Pediatrics** for the year ending in October, 1959, and Dr. William W. Belford, of San Diego, Calif., vice-president. The Executive Board members elected for the coming year are: Drs. Richard C. Eley, Boston; George M. Wheatley, New York City; Carl C. Fischer, Philadelphia; William Weston Jr., Columbia, S. C.; James G. Kramer, Akron, Ohio; Harold F. Flanagan, St. Paul, Minn.; Clarence H. Webb, Shreveport, La.; Frank H. Douglass, Seattle; George H. Schade, San Francisco; and Anibal Ariztia, Santiago, Chile.——The **Clinical Orthopaedic Society** has elected the following officers: president, Dr. Atha Thomas, Denver; vice-president, Dr. Robert C. Robertson, Chattanooga, Tenn.; secretary-treasurer, Dr. Charles H. Frantz, Grand Rapids, Mich.; senior member, Dr. Kerwin A. Fischer, Louisville, Ky. (Membership Committee); junior member, Dr. Charles H. Herndon, Cleveland (Membership Committee).

CANADA

Institute for Mentally Ill Accredited.—The Board of Commissioners has approved the recommendation of the American Psychiatric Association that the Albert Prevost Institute, Montreal, be accredited. This is the result of a survey of the premises, a study of the records, and an inspection of all the services made by the inspectors of the Central Inspection Board who published a report to this effect over the signature of Dr. Douglas A. Johnston. The accreditation was granted, the standards being in conformity with the requirements for an institution specialized in the treatment of the mentally ill.

Surgeons Meet in Vancouver.—Surgeons and related medical personnel are invited to attend the three-day Sectional Meeting of the American College of Surgeons in Vancouver, British Columbia, Feb. 26-28, 1959. Headquarters will be the Hotel Vancouver. The program will include reports on plastic surgery of the hand, varicose veins, the bad risk surgical patient, athletic injuries, arterial injuries, the control of diagnostic radiology, treatment of breast cancer, surgical treatment of head and neck cancer, and diseases of the pancreas. Symposiums on infections, trauma, and cancer will be presented. Selected medical motion pictures and cine clinic films from the 1958 clinical congress will be shown. Dr. William L. Sloan, Vancouver, will represent the American College of Radiology in his report on Thursday afternoon which is one of a series being presented at each of the 1959 Sectional Meetings of the American College of Surgeons, as a cooperative program between both colleges on the subject of patient exposure from diagnostic x-ray. On Saturday the program will emanate from Vancouver General Hospital. Canadian doctors will present reports on cancer of the thyroid gland, parathyroid tumors, parotid tumors, hip fractures, and frozen sections in surgery. Dr. H. Prather Saunders, Associate Director, the American College of Surgeons, 40 E. Erie St., Chicago 11, is in charge of all sectional meetings for the college.

FOREIGN

Meeting on Pneumoconioses.—Experts from 10 countries met recently at the International Labor Organization headquarters, Geneva, Switzerland, on the international classification of radiographs of pneumoconioses. The agenda was opened by Mr. Abbas Ammar, assistant director-general of the International Labor Organization. Prof. Gernez-Rieux, director of the Pasteur Institute at Lille, was elected chairman of the meeting. The experts came from Belgium, France, the Federal Republic of Germany, Italy, Poland, Switzerland, the Union of South Africa, the United Kingdom, the United States, and the U. S. S. R. Representing the U. S. was Dr. Robert H. Flinn, chief, Division of the Health, Bureau of Mines, the Department of the Interior.

CORRECTION

Myocardial Failure in Toxemia of Pregnancy.—In the Dec. 20, 1958, issue of THE JOURNAL, page 2191, the sixth word in the 28th line of the Medical Literature Abstract entitled "Myocardial Failure in Toxemia of Pregnancy," should have read "ST" rather than "5T."

EXAMINATIONS AND LICENSURE

NATIONAL BOARD OF MEDICAL EXAMINERS

National Board of Medical Examiners: Part II only, April 21-22; Parts I and II, June 16-17; Part I only, Sept. 9-10. Examinations must be received at least six weeks in advance of a specific examination date. Examining centers established after close of registration. Exec. Sec., Dr. John P. Hubbard, 133 South 36th St., Philadelphia 4.

EDUCATIONAL COUNCIL FOR FOREIGN MEDICAL GRADUATES, INC.

Educational Council for Foreign Medical Graduates, Inc.: Stations around the world, Feb. 17. Deadline for foreign applications was Nov. 17. The following examination will be held Sept. 22 with application deadline of June 22. Exec. Director, Dr. Dean F. Smiley, 1710 Orrington Ave., Evanston, Ill.

BOARDS OF MEDICAL EXAMINERS

ALABAMA: *Written.* Montgomery, June 16-18. Sec., Dr. D. G. Gill, State Office Bldg., Montgomery 4.

ALASKA:* On application in Anchorage and Juneau. Sec., Dr. W. M. Whitehead, 172 South Franklin St., Juneau.

ARIZONA:* *Written Examination and Reciprocity.* Phoenix, Jan. 14-16. Sec., Dr. Thomas H. Bate, 2910 North 7th Ave., Phoenix.

ARKANSAS:* *Examination and Reciprocity.* Little Rock, June 11-12. Sec., Dr. Joe Verser, Harrisburg.

CONNECTICUT:* *Regular. Examination.* Hartford, March 10-12. Acting Sec., Dr. Louis P. Hastings, 160 St. Ronan St., New Haven. *Homeopathic. Examination.* Derby, Jan. 13. Sec., Dr. Donald A. Davis, 38 Elizabeth St., Derby.

DELAWARE: *Written Examination and Endorsement.* Dover, Jan. 13-15, Jan. 22. Sec., Dr. Joseph S. McDaniel, Professional Bldg., Dover.

FLORIDA:* *Examination.* Miami Beach, June 22-24. Sec., Dr. Homer L. Pearson, 901 N.W. 17th St., Miami 36.

GEORGIA: *Examination and Reciprocity.* Atlanta, June. Sec., Mr. C. L. Clifton, 224 State Capitol, Atlanta 3.

GUAM: *Subject to Call.* Act. Sec., Dr. F. L. Conklin, Agana.

HAWAII: *Examination.* Honolulu, Jan. 12-13. Sec., Dr. I. L. Tilden, 1020 Kapiolani St., Honolulu.

IDAHO: *Examination and Endorsement.* Boise, Jan. 12-14. Sec., Mr. Armand L. Bird, 364 Sonna Bldg., Boise.

ILLINOIS: *Examination and Reciprocity.* Chicago, Jan. 26-30. Supt. of Registration, Mr. Fredric B. Selcke, Capitol Bldg., Springfield.

KANSAS:* *Examination.* Kansas City, Jan. 16-17. *Reciprocity.* Kansas City, Jan. 14. Sec., Dr. F. J. Nash, 364 New Brotherhood Bldg., Kansas City.

MAINE: *Examination.* Portland, March 10-12. *Endorsement.* Portland, March 12. Sec., Dr. Adam P. Leighton, 142 High St., Portland.

MASSACHUSETTS: *Examination.* Boston, Jan. 13-16. Sec., Dr. Robert C. Cochrane, State House, Room 37, Boston 33.

MINNESOTA:* *Examination.* Minneapolis, Jan. 20-22. *Reciprocity.* St. Paul, February. Sec., Dr. F. H. Magney, 230 Lowry Medical Arts Bldg., St. Paul.

MISSOURI: *Examination.* Kansas City, Jan. 9-10. Exec. Sec., Mr. John A. Hailey, Box 4, Jefferson City.

MONTANA: *Examination and Reciprocity.* Helena, April 7. Sec., Dr. Thomas L. Hawkins, 555 Fuller Ave., Helena.

NEBRASKA:* *Examination.* Omaha, June. Director, Mr. Husted K. Watson, Room 1009, State Capitol Bldg., Lincoln 9.

NEW HAMPSHIRE: *Examination and Endorsement.* Concord, Mar. 11-14. Sec., Dr. Edw. W. Colby, 61 So. State St., Concord.

NEW MEXICO:* *Examination and Reciprocity.* Sante Fe, May 18-19. Sec., Dr. R. C. Derbyshire, 227 East Palace Ave., Santa Fe.

NEW JERSEY: *Examination.* Trenton, Jan. 20-23. Sec., Dr. Royal A. Schaaf, 28 W. State St., Trenton.

NORTH CAROLINA: *Reciprocity.* Southern Pines, Jan. 17. *Examination.* June. Asst. Sec., Mrs. Louise J. McNeill, 716 Professional Bldg., Raleigh.

NORTH DAKOTA: *Examination and Reciprocity.* Grand Forks, Jan. 7-10. Sec., Dr. C. J. Glaspel, Grafton.

OKLAHOMA:* *Examination.* Oklahoma City, June 2-3. Exec. Sec., Mrs. E. L. Haidek, 813 Braniff Bldg., Oklahoma City.

OREGON:* *Examination.* Portland, Jan. 6-7. *Reciprocity.* Portland, Jan. 8-10. Exec. Sec., Mr. Howard I. Bobbitt, 609 Failing Bldg., Portland 4.

PENNSYLVANIA: *Examination.* Philadelphia, Jan. 7-10. Sec., Mrs. Margaret G. Steiner, Box 911, Harrisburg.

PUERTO RICO: *Examination and Reciprocity.* San Juan, March 3. Acting Secretary, Dr. Herminio Mendez Herrera, Box 9156, Santurce.

RHODE ISLAND:* *Examination.* Providence, Jan. 8-9. Admin., Division of Professional Regulation, Mr. Thomas B. Casey, 366 State Office Bldg., Providence.

SOUTH DAKOTA:* *Examination.* Sioux Falls, Jan. 20-21. Exec. Sec., Mr. John C. Foster, 300 First National Bank Bldg., Sioux Falls.

UTAH: *Examination.* Salt Lake City, July 8-10. Dir., Mr. Frank E. Lees, 324 State Capitol Bldg., Salt Lake City 1.

WASHINGTON:* *Examination.* Seattle, Jan. 12-14. Sec., Mr. Thomas A. Carter, Capitol Bldg., Olympia.

WEST VIRGINIA: *Examination and Reciprocity.* Charleston, Jan. 5-7. Sec., Dr. Newman H. Dyer, State Office Bldg. No. 3, Charleston 5.

WISCONSIN:* *Examination and Reciprocity.* Madison, Jan. 13-15. Sec., Dr. Thomas W. Tormey, Jr., 1140 State Office Bldg., 1 West Wilson St., Madison.

WYOMING: *Examination and Reciprocity.* Cheyenne, Feb. 2. Sec., Dr. Franklin D. Yoder, State Office Bldg., Cheyenne.

BOARDS OF EXAMINERS IN THE BASIC SCIENCES

ARKANSAS: *Examination.* Little Rock, May 4-5. Sec., Dr. S. C. Dellinger, University of Arkansas, Fayetteville.

CONNECTICUT: *Examination.* New Haven, Feb. 14. Exec. Asst., Mrs. Regina G. Brown, 258 Bradley St., New Haven 10.

FLORIDA: *Examination.* Miami, June 6. Sec., Mr. M. W. Emmel, University of Florida, Box 340, Gainesville.

IOWA: *Examination.* Des Moines, Jan. 13. Sec., Dr. Elmer W. Hertel, Wartburg College, Waverly.

KANSAS: *Examination.* Kansas City, June. Sec., Dr. L. C. Heckert, Pittsburg.

MICHIGAN: *Examination.* Ann Arbor and Detroit, Feb. 12-13. Sec., Mrs. Anne Baker, 116 Stevens T. Mason Bldg., West Michigan Ave., Lansing.

MINNESOTA: *Examination.* Minneapolis, Jan. 6-7. Sec., Dr. Raymond N. Bieter, 105 Millard Hall, University of Minnesota, Minneapolis 14.

NEW MEXICO: *Examination.* Santa Fe, Jan. 18. Sec., Mrs. Marguerite Cantrell, Box 1522, Santa Fe.

OKLAHOMA: *Examination.* Oklahoma City, Mar. 27-28. Exec. Sec., Mrs. L. Haidek, 813 Braniff Bldg., Oklahoma City.

RHODE ISLAND: *Examination.* Providence, Feb. 18. Administrator of Professional Regulation, Mr. Thomas B. Casey, 366 State Office Bldg., Providence.

TENNESSEE: *Examination.* Memphis, Dec. 31-Jan. 1. Sec., Dr. O. W. Hyman, 62 South Dunlap St., Memphis 3.

TEXAS: *Examination.* April 1959. Certificates issued by reciprocity and waiver on the first and fifteenth of each month. Sec., Bro. Raphael Wilson, 407 Perry-Brooks Bldg., Austin.

WASHINGTON: *Examination.* Seattle, Jan. 7-8. Sec., Mr. Thomas A. Carter, Capitol Bldg., Olympia.

*Basic Science Certificate required.

GOVERNMENT SERVICES

AIR FORCE

Award of Commendation Medal.—Lieut. Col. Frederick S. Spiegel, M. C., recently was presented the Air Force Commendation medal by the director of professional services in the surgeon general's office. Doctor Spiegel was cited for planning and putting into operation a new procedure for processing of medical examinations for Air Force Academy candidates for the class of 1962 and developing new procedures and establishing additional centers for administration of medical examinations. He is a senior flight surgeon and is board-certified in aviation medicine.

SOCIAL SECURITY

Disability Evaluation.—The Social Security Administration's Medical Advisory Committee has developed, with the cooperation of the medical professions, a sound and workable method of determining disability. This difficult task has been accomplished in a way which does not interfere with doctor-patient relationships. The social security law provides monthly disability insurance payments for disabled persons aged 50 or over and for their dependents. Those who are disabled before reaching 50 years may "freeze" their social security records to prevent their future benefits from being reduced or lost entirely. Under the law, a person is considered disabled if he is unable to do any substantial gainful work, and his condition is expected to continue indefinitely. Under the system worked out for determining whether the disability requirement is met, a person who applies for disability insurance benefits or to have his social security record frozen is first asked to get a statement from his physician. The physician is asked to report clinical findings—the results of medical tests and laboratory examinations. The decision as to whether or not the person is disabled is made by a team of trained people, including a physician, in a state agency. They study not only the medical findings but also the person's education and experience. In most states this team is in the state vocational rehabilitation agency. The state vocational rehabilitation agency also considers the possibility of providing rehabilitation services to the disabled person. Thus the social security disability program has provided a new opportunity for getting more disabled people in touch with rehabilitation agencies. Disability evaluation is not a static process but must keep pace with medical progress, according to Secretary Fleming.

PUBLIC HEALTH SERVICE

Neuropharmacology Research Center.—The new research center for the study of drugs and their use in the treatment of mental illness which was opened Nov. 20 at Saint Elizabeths Hospital, Washington, D. C., will be operated jointly by Saint Elizabeths and the U. S. Public Health Service's National Institute of Mental Health. This clinical research center is being set up in the William A. White Building, which has been adapted to accommodate the research facilities and which houses 350 patients. The center is being equipped for a comprehensive, scientific assessment of the tranquilizing and energizing drugs and their effects on mental function.

Dr. Joel Elkes, National Institute of Mental Health pharmacologist and former chairman, department of experimental psychiatry, University of Birmingham in England, is director of the center.

Dr. Winfred Overholser, superintendent of Saint Elizabeths, said "This program, I believe, holds particular promise not only for Saint Elizabeths but for psychiatry in general. I am confident that this carefully planned research undertaking will bring forth knowledge that will guide us in the use of drugs and from which new effective treatment methods will evolve." Working together on the project will be psychiatrists, psychologists, pharmacologists, biochemists, physiologists, and other research specialists.

Neurologists' Mission to the Soviet Union.—In accord with an agreement between the United States and the Soviet Union to exchange missions in various fields, the National Institute of Neurological Diseases and Blindness is sponsoring a study team of six American scientists who will survey the status of neurology in the Soviet Union. The study team departed for Russia, Nov. 18, and will remain there about 30 days. The members of the mission are Dr. Francis M. Forster, chairman, department of neurology, Wisconsin University School of Medicine; Dr. Nathan Woolsey, research professor of neurophysiology, University of Wisconsin; Dr. Paul I. Yakovlev, professor of neuropathology at Harvard University Medical School; Dr. Louis S. Goodman, professor of pharmacology, Utah University School of Medicine; Dr. Henry W. Woltman, professor of neurology, Mayo Foundation Graduate School; and Dr. Karl Frank, neurophysiologist, National Institute of Neurological Diseases and Blindness, National Institutes of Health. A group of Soviet specialists will make a similar study on neurology in the United States at a later date.

DEATHS

Abbott, Leigh Gates Ⓜ Orleans, Vt.; University of Vermont College of Medicine, Burlington, 1945; certified by the National Board of Medical Examiners; specialist certified by the American Board of Surgery; veteran of World War II; interned at Worcester City Hospital in Worcester, Mass., and served a residency at St. Vincent Hospital in Worcester; captain in the medical reserve corps of the U. S. Army from July 8, 1946 to July 2, 1948; member of the school board; on the staffs of the Broadview General Hospital and Orleans County Memorial Hospital in Newport Oct. 15, aged 35, of coronary thrombosis.

Andress, David Gustavus Ⓜ Madrid, Ala.; Chattanooga (Tenn.) Medical College, 1904; at one time president of the Bank of Madrid; in 1954 was awarded a certificate of merit by the Medical Association of the State of Alabama in recognition of 50 years service as a practicing physician; died Oct. 15, aged 83.

Bailey, Hugh Alvin Ⓜ Charleston, W. Va.; born in Vass, N. C., Dec. 4, 1900; University of Maryland School of Medicine and College of Physicians and Surgeons, Baltimore, 1928; specialist certified by the American Board of Surgery; member of the Southern Surgical Association and the Southeastern Surgical Congress; fellow of the American College of Surgeons and co-founder and first president of the West Virginia Chapter; consulting surgeon at Memorial, Kanawha Valley, and Staats hospitals in Charleston, and visiting surgeon at Mountain State, St. Francis, and McMillan hospitals; died in a hospital in Baltimore Oct. 25, aged 57, following an operation for cancer of the lung.

Ballard, Robert Jackson, Michigan City, Ind.; Indiana University School of Medicine, Indianapolis, 1942; on the staffs of St. Anthony Hospital in Michigan City, and the Dr. Norman M. Beatty Memorial Hospital in Westville; died July 9, aged 42, of injuries received when his automobile was struck by a train.

Benson, Harry William, Winter Park, Fla.; University of Nebraska College of Medicine, Omaha, 1903; an associate member of the American Medical Association; for nine years a trustee of the Nebraska State Medical Association and in 1952 the organization gave him a distinguished service medal and made him a member emeritus; member of the American Academy of General Practice and one of the founders and past-president of the Nebraska Section; in 1926 was president of the Oakland, Neb., Chamber of Commerce; died in Orlando Oct. 15, aged 82, of thrombosis.

Blackburn, Elisha, Worthington, Ohio; University of Wooster Medical Department, Cleveland, 1903; served as a medical missionary in Africa; died in the Jeanes Hospital, Philadelphia, Oct. 12, aged 85, of arteriosclerosis.

Blankenship, Marvin Winfred Ⓜ Fulton, Ky.; University of Tennessee College of Medicine, Memphis, 1951; interned at the Baptist Memorial Hospital in Memphis, Tenn.; veteran of World War II; co-owner of the Hillview Hospital; accidentally shot and killed by a deer hunter in Grand Junction, Colo., Oct. 17, aged 34.

Bohannan, Hugh Russell Ⓜ Jerseyville, Ill.; Illinois Medical College, Chicago, 1904; past-president of the Jersey County Medical Society; director of the Jersey Savings & Loan Company with which he was associated for over 39 years; died in St. Joseph's Hospital Oct. 20, aged 82, of a cerebrovascular accident.

Boiarsky, Julius Lewis Ⓜ Charleston, W. Va.; Duke University School of Medicine, Durham, N. C., 1935; interned at the Deaconess Hospital in Cincinnati and served a residency at Charleston General Hospital; veteran of World War II; founder and director of the Boiarsky Memorial Hospital; died Oct. 29, aged 51.

Brockway, Porter Bruce Ⓜ Toledo, Ohio; Rush Medical College, Chicago, 1900; member of the House of Delegates of the American Medical Association in 1911; member of the Academy of Medicine of Toledo and Lucas County and the American Public Health Association; veteran of World War I; founder of the health department in the public schools of Toledo, where he served for 33 years as director of health; chief of staff and board member of the Flower Hospital; associated with Toledo Hospital, St. Charles Hospital, and Maumee Valley Hospital, died Oct. 28, aged 83, of coronary insufficiency.

Butterfield, Clarence Egbert Ⓜ Concord, N. H.; Dartmouth Medical School, Hanover, N. H., 1903; on the emeritus staff, Concord Hospital, where he died Oct. 16, aged 82, of coronary thrombosis.

Clark, Harold Chandler, New Rochelle, N. Y.; University of Maryland School of Medicine and College of Physicians and Surgeons, Baltimore, 1918;

Ⓜ Indicates Member of the American Medical Association.

member of the Medical Society of the State of New York and the American Academy of Pediatrics; associated with the New Rochelle Hospital, where he died Oct. 22, aged 65.

Clifton, Willie Mae, Northfield, Ill.; Woman's Medical College of Pennsylvania, Philadelphia, 1932; specialist certified by the American Board of Pediatrics; interned at the Bethesda Hospital in Cincinnati; served a residency at the Children's Memorial Hospital in Chicago, where she was on the attending staff; died in the Evanston (Ill.) Hospital Sept. 27, aged 52, of heart failure due to mitral insufficiency.

Coburn, Henry Clay Jr. ℞ Brigadier General, U. S. Army, retired, Haddonfield, N. J.; born in Washington, D. C., Aug. 5, 1879; Columbian University Medical Department, Washington, D. C., 1903; entered the medical corps of the U. S. Army in 1909 and saw service in the Philippines and North China from 1910 to 1913; served in France during World War I; chief of medical service at Walter Reed General Hospital, Washington, D. C., from 1935 to 1939, before which he had held similar posts at Fitzsimons General Hospital, Denver, and the U. S. Army Hospital at Fort Sam Houston, Texas; his last active duty assignment before retiring in 1946 was as surgeon at Fort Bragg, N. C.; retired Aug. 31, 1943; retained on active duty until Jan. 20, 1946; held the Legion of Merit and the French Legion of Honor; specialist certified by the American Board of Internal Medicine; service member of the American Medical Association; fellow of the American College of Surgeons and the American College of Physicians; died Oct. 22, aged 79, of coronary thrombosis and arteriosclerosis.

Cochran, Athol ℞ Joplin, Mo.; Memphis (Tenn.) Hospital Medical College, 1901; member of the Kansas Medical Society; also a minister; formerly practiced in Pratt, Kan., where he was associated with the Ninnescah Hospital; died in the Barton County Memorial Hospital, Lamar, Oct. 19, aged 81, of injuries received in an automobile accident.

Cooley, Ben Hunter ℞ El Paso, Texas; University of Oklahoma School of Medicine, Oklahoma City, 1921; veteran of World Wars I and II; fellow of the American College of Physicians; past-vice-president of the Texas Heart Association; associated with the Southwestern General and Providence Memorial hospitals and the Hotel Dieu, Sisters' Hospital; died Sept. 20, aged 63.

Cuff, John Reginald, Nashville, Tenn.; Meharry Medical College, Nashville, Tenn., 1926; professor of pathology at his alma mater; certified by the National Board of Medical Examiners; specialist certified by the American Board of Pathology; died in the Hubbard Hospital Oct. 22, aged 64, of cancer of the stomach.

Elkin, Daniel Collier, Lancaster, Ky.; born in Louisville March 26, 1893; Emory University School of Medicine, Atlanta, 1920; served an internship and residency at the Peter Bent Brigham Hospital in Boston, where he became an assistant in surgery at Harvard Medical School; professor emeritus of surgery at his alma mater, where he joined the faculty as instructor of surgery in 1923, subsequently serving as associate in surgery and for 23 years professor and chairman of the department of surgery; in 1939, when it was established, became Joseph Brown Whitehead professor of surgery; visiting professor at the University of Virginia School of Medicine in Charlottesville, University of Michigan Medical School, Ann Arbor, and Harvard Medical School in Boston; chairman, Section on Surgery, General and Abdominal, American Medical Association, from 1944 to 1946; past-president of the American College of Surgeons (of which he was a regent), the Society of Vascular Surgery, Society of Medical Consultants, Southern Surgical Association, American Surgical Association, of which he was past-vice-president, and the Society of Clinical Surgery; member of the International Society of Surgeons, and senior member of the American Association for Thoracic Surgery; member of the founders group of the American Board of Surgery; specialist certified by the Board of Thoracic Surgery; during World War II spent more than three years as chief of the surgical section and chief of professional services at Ashford General Hospital, White Sulphur Springs, W. Va.; released from active duty as a colonel in 1946 and in 1949 was promoted to brigadier general in the reserve; later consultant in surgery to the surgeon general, chief civilian consultant in surgery for the Third Army, and consultant to the Walter Reed Army Medical Center, Washington, D. C.; in 1945 was awarded the Legion of Merit for his Army service in which he "developed and standardized methods of diagnosis and introduced new and improved techniques in surgical procedure on wounds of the blood vessels"; in 1940 he became the third man to be awarded the Matas Medal by Tulane University for "conspicuous achievements in advancing the progress of vascular surgery"; in 1954, at the 104th annual meeting of the Medical Association of Georgia in Macon, received the Lamartine Griffin Hardman award for "distinguished service to the science of medicine and the medical profession in Georgia" and for "exceptional work in the field of vascular surgery"; from 1939 to 1948 surgeon-in-chief of the Grady Memorial Hospital; served as surgeon in chief of the Henrietta Egleston Hospital for Children; member of the founders group of the American Board of Surgery; specialist certified by the Board of Thoracic Surgery; special consultant to the U. S. Public Health Service (National Institutes of Health) and chairman of the subcommittee on vascular surgery of the National Re-

search Council; a member of the committee on medical affairs of Yale University in New Haven, Conn., and a trustee of the University of Kentucky, Lexington; held an honorary doctor of science degree from Northwestern University in Chicago; author of many papers on surgical subjects; died Nov. 3, aged 65, of heart disease.

Grube, Orin Charles, Minneapolis; State University of Iowa College of Medicine, Iowa City, 1957; interned at Broadlawns Polk County Hospital in Des Moines; died in the University Hospitals, Iowa City, Sept. 19, aged 26.

Herbst, Richard Fred Ⓜ Willmar, Minn.; University of Minnesota Medical School, Minneapolis, 1933; on the staffs of the Willmar State Hospital and the Rice Memorial Hospital, where he died Oct. 5, aged 50, of electrolytic imbalance.

Hindman, Sims Seward, Waynesville, N. C.; Vanderbilt University School of Medicine, Nashville, Tenn., 1900; veteran of the Spanish–American War; for many years practiced in Toledo, Ohio, where he was on the staff of the Riverside Hospital; on the staff of the Haywood Hospital; died in the Wyandotte (Mich.) General Hospital Oct. 6, aged 79, of cerebrovascular accident.

Jackson, Isaiah Allen, Richmond, Va.; Leonard Medical School, Medical Department of Shaw University, Raleigh, N. C., 1911; served on the staff of the Richmond Community Hospital, of which he was one of the founders; on the courtesy staff of Richmond Memorial Hospital; died Oct. 28, aged 70.

Jacobson, Arthur Clarence, Brooklyn; born in Brooklyn Sept. 28, 1872; Long Island College Hospital, Brooklyn, 1894; an associate member of the American Medical Association; member of the American Academy of General Practice, American Association for the Advancement of Science, Medical Library Association, Associated Physicians of Long Island, Alumni Association of Brooklyn Hospital and Long Island College Hospital; medical inspector of city schools, department of health, New York City, 1899; physician, department of public welfare, New York City, from 1900 to 1929; physician, department of hospitals, New York City, from 1929 to 1945; author of "Genius–Some Revaluations," published in 1926; in 1927 became editor of the *Medical Times,* serving until he was named editor-in-chief emeritus last January; died in the Brooklyn Hospital Oct. 15, aged 86, of uremia, secondary to arteriosclerotic cardiovascular disease and diverticulitis with abscess and hemorrhage.

Joseph, Cheney Cleveland Ⓜ Baton Rouge, La.; Tulane University School of Medicine, New Orleans, 1938; specialist certified by the American Board of Internal Medicine; member of the American College of Chest Physicians; medical director of the United Security Life Insurance Company; veteran of World War II; on the staffs of Our Lady of the Lake Hospital and the Baton Rouge General Hospital, where he died Oct. 13, aged 44, of an accidental gunshot wound of the brain.

Keating, Robert Alfred Ⓜ Columbus, Ohio; Ohio State University College of Medicine, Columbus, 1937; assistant professor of surgery at his alma mater; fellow of the American College of Surgeons; member of the Columbus Academy of Medicine; veteran of World War II; associated with University, Mount Carmel, Children's, and White Cross hospitals; died in Milwaukee, where he was attending a medical meeting Oct. 7, aged 47, of coronary occlusion.

Kennedy, J. Edward T., Cincinnati; Ohio–Miami Medical College of the University of Cincinnati, 1913; veteran of World War I and was awarded the Belgian Croix de Guerre by the king; for many years police and fire surgeon; formerly associated with the U. S. Public Health Service; served as vice-president of the Good Samaritan Hospital and chief of the medical staff, Deaconess Hospital; rating specialist for the Veterans Administration Hospital; died in the Veterans Administration Hospital Oct. 1, aged 72, of a heart attack.

Manwaring, Ier Jay Ⓜ Norwich, Conn.; Woman's Medical College of Pennsylvania, Philadelphia, 1895; during World War I, as a member of the American Women's Hospital unit number 1, was attached to a division of the French Army and served in France for 14 months; in April, 1919, was decorated by the French government for service at Chateau Thierry and Belleau Wood; died in the William W. Backus Hospital Oct. 3, aged 85.

Martin, Charles Dyer, Davenport, Iowa; Marquette University School of Medicine, Milwaukee, 1917; veteran of World War I; found dead in a hotel room at Chattanooga, Tenn., Oct. 13, aged 65, of heart disease.

Sands, Irving Jesse Ⓜ Brooklyn; born in Russia March 27, 1891; Columbia University College of Physicians and Surgeons, New York City, 1913; served on the faculty of his alma mater; specialist certified by the American Board of Psychiatry and Neurology; fellow of the American College of Physicians, New York Academy of Medicine, and the American Psychiatric Association; member of the American Neurological Association, American Psychoanalytic Association, American Academy of Neurology, American Psychosomatic Society, American Geriatrics Society, and the Association for Research in Nervous and Mental Disease; past-president of the New York Neurological Society; panel psychiatrist for the board of education and honorary police surgeon; consultant for the New York State Workmen's Compensation board; author

of "Abnormal Behavior" and "Neuropsychiatry for Nurses"; on the associate editorial board, *New York State Journal of Medicine;* consultant at Veterans Administration; associated with the Rockaway Beach and St. Joseph hospitals in Far Rockaway, Hillside Hospital in Bellerose, New York Neurological Institute of the Columbia–Presbyterian Medical Center in New York City, Adelphi, Brooklyn State, Prospect Heights, Women's, Kingston Avenue, Coney Island, Beth El, and Jewish Chronic Disease hospitals, and the Jewish Hospital, where he was head of the medical board and where he died Oct. 21, aged 67, of myocardial infarction.

Sawyer, Matthias Harvey ⊛ Ottawa, Ill.; Sioux City (Iowa) College of Medicine, 1904; past-president of the La Salle County Medical Society; at one time health officer of Ottawa; county coroner from 1950 to 1952; on the honorary staff of Ryburn Memorial Hospital, where he died Oct. 13, aged 79, of bronchopneumonia.

Scott, Edwin Laurence, Ocala, Fla.; University of Maryland School of Medicine, Baltimore, 1906; member of the American Orthopaedic Association; formerly practiced in Birmingham, Ala., where he was one of the founders of the Crippled Children's Clinic; recently honored with a citation from the Florida Association of Insurance Agents; died Oct. 10, aged 74, of cancer.

Shaw, Henry Alden ⊛ Colonel, U. S. Army, retired, Rutland, Mass.; born in New Salem, Mass., June 3, 1867; Harvard Medical School, Boston, 1890; service member of the American Medical Association; fellow of the American College of Surgeons; served an internship at the Massachusetts General Hospital in Boston, then entered the U. S. Army Medical Corps in which he served for thirty years' service before retiring in 1921; decorated with the Distinguished Service Medal; officier, Legion of Honor, France; veteran of World War I; assistant in bacteriology, University of Minnesota Medical School, Minneapolis, 1896-1897; assistant in surgery, Army Medical School, Washington, D. C., 1902-1903; professor of military hygiene, U. S. Military Academy, West Point, N. Y., from 1914 to 1917; sanitary advisor, League of Red Cross Societies Commission to Poland, Warsaw, 1920-1921; in charge of the hospital division of the Veterans Bureau in Washington, D. C., in 1921; psychiatrist and assistant professor of mental hygiene at his alma mater from 1925 to 1934; the following year became psychiatrist in the outpatient department at the New York Hospital; died in the Holden District Hospital, Haydenville, Oct. 19, aged 91.

Shumway, John Raymond, Pleasanton, Kan.; University Medical College of Kansas City, Mo., 1901; served as health officer and coroner of Linn County; on the staff of Mercy Hospital in Fort Scott; died Oct. 1, aged 80, of cerebral hemorrhage.

Southard, Jefferson Sherlock, Fort Smith, Ark.; Tulane University of Louisiana School of Medicine, New Orleans, 1922; veteran of World War I; past-president of the Sebastian County Medical Society; died in Little Rock Oct. 8, aged 63.

Speight, James Ambler, Rocky Mount, N. C.; Tulane University of Louisiana School of Medicine, New Orleans, 1914; member of the Medical Society of the State of North Carolina; formerly county health officer; for services rendered in World War II was awarded a Selective Service Medal; Speight–Stone Clinic is now known as the Memorial Hospital; associated with Park View Hospital; died Oct. 1, aged 68, of heart disease and cirrhosis of the liver.

Stapleton, Harvey Burr ⊛ Hickman, Neb.; Creighton University School of Medicine, Omaha, 1917; veteran of World War I; member of the American Academy of General Practice; died in Lincoln Oct. 1, aged 68, of coronary thrombosis.

Strode, George King, Whitingham, Vt.; born in Chadds Ford, Pa., Jan. 16, 1886; University of Pennsylvania School of Medicine, Philadelphia, 1912; received master's degree in public health at Harvard in 1927; served as hygienist of the Pennsylvania State Department of Health in Harrisburg; member of the International Health Division of the Rockefeller Foundation since 1920, having been chosen a member for one year in 1916; served as director from 1944 until his retirement in 1951; stationed in Brazil for the division from 1920 to 1926; assistant director from 1927 to 1938 in charge of the division's activities in Europe, Africa, and the Near East, with headquarters in Paris; chairman of the foundation's Paris office from 1932 to 1938, when he became associate director; captain in the medical corps of the U. S. Army, serving in France during World War I; member of the American Red Cross missions during World War II, to Russia in 1941, Iceland in 1942, and North Africa in 1942-1943; during the war was also a member of the advisory council of the division of health and sanitation, of the Institute of Inter-American Affairs, of the subcommittee on tropical diseases on the National Research Council, and of the subcommittee on tropical diseases of the health advisory committee, Office of Foreign and Rehabilitation Operations; an honorary fellow of the Society of Medical Officers of Health of Great Britain; fellow of the American Public Health Association; a member of the American Society of Tropical Medicine, American Academy of Tropical Medicine, of which he was past-vice-president, American Association for the Advancement of Science, and the New York Society of Tropical Medicine; decorated by the governments of Norway, Denmark, Bulgaria, Portugal, France, Rumania, and Sweden; editor of "Yellow Fever," published in 1951; "The Story of the Rockefeller Foundation" by Raymond B. Fosdick published in 1952 praised his work; died in

the Brattleboro (Vt.) Memorial Hospital Oct. 27, aged 72, of adenocarcinoma of bladder with metastases.

Sturkey, Edgar Lafayette, Augusta, Ga.; University of Georgia Medical Department, Augusta, 1906; served on the staffs of various Veterans Administration hospitals; died in the Veterans Administration Hospital Oct. 9, aged 76.

Sullivan, Thomas Henry ⑨ Fall River, Mass.; Middlesex College of Medicine and Surgery, Cambridge, 1930; member of the American Academy of General Practice; associate medical examiner for the greater Fall River area; during World War II served as assistant regimental surgeon with the rank of captain in the medical corps of the Second Armored Division; participated in the African campaign and the invasion of Normandy; decorated by the governments of Belgium and the Netherlands and held a presidential citation; died Oct. 12, aged 56.

Sunderland, Paul Ulysses ⑨ Danbury, Conn.; New York Homeopathic Medical College and Flower Hospital, New York City, 1894; on April 30, 1957, the Connecticut State Medical Society honored him with a 50-year membership citation; on the staff of the Danbury Hospital; died Oct. 9, aged 89, of arteriosclerotic heart disease.

Swartsel, Samuel Carey, San Diego, Calif.; Medical College of Ohio, Cincinnati, 1897; recipient of distinguished service award from the American Cancer Society in 1951; at one time practiced in Cincinnati, where he was past-president of the Cincinnati Medical Society; died Oct. 10, aged 90.

Taylor, Richard Francis, Philadelphia; Jefferson Medical College of Philadelphia, 1905; affiliated with Jefferson and Lankenau hospitals; at one time police surgeon; served on the draft board during World War I; died Oct. 25, aged 79, of heart disease.

Terry, Ernest Alden Jr. ⑨ Louisville, Ky.; Columbia University College of Physicians and Surgeons, New York City, 1945; certified by the National Board of Medical Examiners; member of the American Academy of Occupational Medicine and the Industrial Medical Association, of which he was counselor; assistant professor of community health, University of Louisville School of Medicine; served in the U. S. Naval Reserve from April, 1946, to April, 1948, and again from September, 1950, to March, 1951; medical director of the General Electric Appliance Park Plant; aged 38; was shot and killed Oct. 26, by a former company employee.

Thomas, Napoleon Roscoe ⑨ Albany, Ga.; Atlanta School of Medicine, 1913; veteran of World War I; served as chief of obstetrics and chief of staff at the Phoebe Putney Memorial Hospital; died Oct. 2, aged 76, of cerebral thrombosis and arteriosclerosis.

Thompson, Joseph Ignatius A., Margate City, N. J.; Hahnemann Medical College and Hospital of Philadelphia, 1904; died Oct. 12, aged 75.

Tucker, Adam Reynold, Raleigh, N. C.; Southern College of Medicine and Surgery, Atlanta, 1912; a founder of the Mary Elizabeth Hospital; died Oct. 19, aged 80, of pneumonia.

Tucker, Augustine Washington, Charlottesville, Va.; born in 1883; University of Virginia Department of Medicine, Charlottesville, 1905; fellow of the American College of Surgeons; professor of surgery at St. John's University in Shanghai, China, where he was associated with St. Luke's Hospital; for many years medical missionary of the Protestant Episcopal Church to China; during World War I served in Siberia with the American Red Cross; at one time superintendent of St. Agnes Hospital in Raleigh, N. C.; from 1950 to 1954 school physician at Woodberry Forest; died in the Blue Ridge Sanatorium Oct. 4, aged 75, of pulmonary tuberculosis.

Warren, Alexander M., Rose City, Mich.; Saginaw (Mich.) Valley Medical College, 1902; died Oct. 6, aged 84, of carcinomatosis.

Watkins, Leon Harlan, Pasadena, Calif.; Johns Hopkins University School of Medicine, Baltimore, 1909; an associate member of the American Medical Association; died Oct. 9, aged 75, of uremia and nephritis.

Watts, Charles Edward ⑨ Seattle; born in 1889; Rush Medical College, Chicago, 1918; clinical professor of medicine at University of Washington School of Medicine; past-president of the Washington State Medical Association, King County Medical Society, North Pacific Society of Internal Medicine, and the Pacific Inter-Urban Clinical Club; first president of the Washington State Health Council; active in the Washington State Heart Association and served as vice-president of the American Heart Association; fellow of the American College of Physicians, serving on the board of governors from 1935 to 1947 and as vice-president in 1948-1949; during World War II served in the medical corps of the U. S. Naval Reserve; for many years consultant at the U. S. Public Health Service Hospital and the Veterans Administration Hospital; served as chief of medical services at Harborview Hospital; on the staffs of the Maynard Hospital and the Swedish Hospital, where he died Oct. 12, aged 68, of cerebral thrombosis, cerebral arteriosclerosis, and hypertension.

Wiatt, William Slaughter ⑨ La Jolla, Calif.; Hospital College of Medicine, Louisville, 1897; member of the Missouri State Medical Association; fellow of the American College of Surgeons; served on the faculty of St. Louis University School of Medicine; formerly practiced in St. Louis, where he served on the staff of the Missouri Baptist Hospital; died Oct. 14, aged 86, of cancer of the bladder.

FOREIGN LETTERS

BELGIUM

Iturine.—Delcombe and Devignat (*Annales de la société des sciences médicales*) studied a strain of spore-forming aerobic bacillus which produces in various culture mediums an antibiotic designated as iturine. The bacillus presented all the characteristics of Bacillus subtilis. Two types of colonies isolated differed in their ability to elaborate iturine. The crude products of the cultures could be separated into three fractions. Two of these (O and N) were soluble in acetone, and the third fraction (L) was not. These three fractions were readily differentiated by their antibiotic spectrum, thermostability, and resistance to ultraviolet rays, by paper chromatography, and by dialysis. It is fraction L which has been named iturine. No allergic reaction to this antibiotic has been noted. Clinical tests showed it to be more active than other antifungal agents. About 70% total cures were reported in patients with cutaneous mycoses, with few relapses. Such refractory diseases as epidermophytosis palmaris et plantaris and herpes circinatus have yielded to the drug.

The Postoperative Hiccup.—The postoperative hiccup may appear in different circumstances, and its treatment requires special attention. Reinhold (*Acta anæsthesiologica belgica*) pointed out the harmlessness of the preoperative hiccup, which he treats by aiding respiration. Since the postoperative hiccup is much more alarming, treatment by the inhalation of carbon dioxide infiltration of the phrenic nerve, chlorpromazine, or methamphetamine is recommended. Methamphetamine does not act on the sympathetic nervous system, but rather stimulates the central nervous system. For this reason the author gave 20 mg. of methylphenidate to 12 patients with postoperative hiccup with excellent results in all. The drug was given either intravenously or intramuscularly and no unfavorable side-effects were noted. The action of methylphenidate thus indicates a central origin of hiccups. This drug was especially helpful in old and weak patients in whom chlorpromazine and methamphetamine might cause unfavorable circulatory effects.

Ocular Senescence.—At the 18th International Congress of Ophthalmology in Brussels, Dr. François stated that it was impossible to determine at what age the eye should be considered as being old. Growing old consists of a progressive alteration of the tissular structure, changes that are usually found in the eyes of older persons are considered physiological but those that are found only rarely, although exclusively in the eyes of the aged, are considered pathological. The general senile changes seen in the eye include arteriosclerosis, proliferation of certain tissues, fatty or calcareous infiltration, increase in collagenous tissue, and hyaline degeneration. The degree of these changes varies greatly from one subject to the other and gives no clue to the age of the subject. The sclerotic eye becomes more rigid, and can present a fatty, as well as a calcareous, infiltration. Aging of the lens is associated with a series of changes in its composition, most of which start early in life. In the first years of life, particularly, the concentration of the organic elements become modified, whereas at a more advanced age it is the concentration of the organic substances that changes. Among these latter studies attention was particularly directed toward proteins, which constitute the fundamental substance of the lens fibers.

The items in these letters are contributed by regular correspondents in the various foreign countries.

CANADA

Legal Validity of Breath Tests.—The Supreme Court recently upheld, by a five to three decision, the Saskatchewan provincial legislation compelling suspected drunken drivers to undergo a breath test or face suspension of their driving permit. Mr. Justice Fauteux said that, since a license holder in this condition is in a position similar to that of a person suspected of physical or mental affliction likely to prevent reasonable care and ordinary control of a vehicle, he could be required to submit to an appropriate examination. The refusal to submit to a breath test cannot however be mentioned in court during a charge of drunken or impaired driving, nor can it be made legally compulsory. The main objection to the requirement had been that it conflicted with the criminal code. The three judges in the minority all believed that this was true of the regulation, while the others held that it was not criminal legislation but only a statute relating to the administration and control of the highways.

Experimental Atherosclerosis.—A collaboration between veterinarians and clinicians was described in the *Canadian Medical Association Journal* by Rowsell and co-workers (79:647, 1958). Recent

work suggested that patients with clinical manifestations of atherosclerosis have abnormally active clotting systems. This activity is determined to some extent by the type of fat in the diet. Because butter accelerates clotting in vitro and in vivo, and margarine has little such activity, feeding animals butter could be expected to produce more atherosclerosis than could feeding them margarine. At the Ontario Veterinary College, 33 hogs were divided into three groups and fed a low-fat diet and a diet rich in butter or in margarine respectively. Some atherosclerosis was found in the swine fed a low-fat diet, and this was not greatly increased by adding margarine, but the group fed butter had a marked increase in amount of atherosclerosis. Coagulation indexes at the end of the experiment were most active in the butter-fed swine with the most atherosclerosis. Grossly and microscopically, the atheromas in the swine resembled human lesions.

A further study of coagulation indexes in human subjects by Mustard (*Canad. M. A. J.* 79:736, 1958) produced further evidence linking atherosclerosis with blood coagulation. In this experiment, 135 men were divided into groups of those with clinical complications of atherosclerosis or a family history of the disease and those with no family history and no clinical signs. They were all given a meal of dairy fat and eggs. The atherosclerotic subjects had the greatest mean increase in plasma density and Christmas factor activity, and decrease in antihemophilic globulin activity. The control group had the least changes. It seems that subjects with clinical signs or a family history of atherosclerosis have a more greatly enhanced clotting activity during alimentary lipemia than those with a negative history and no signs.

Alcoholism.—The seminar of the Alcoholism Research Foundation of Ontario included physicians, psychologists, educators, sociologists, psychiatrists, editors, and public relations personnel. It examined the problem of alcoholism almost de novo, asking what the fundamental obstacles were to further understanding of this problem. One of the problems considered was that of setting a threshold above which the regular use of alcohol might be expected to cause harm, either by producing physical or mental impairment or by causing addiction. A forensic expert pointed out the gross discrepancy between the high legal limits for drunkenness (for example, in automobile driving) and the educational limits tacitly admitted in such phrases as "if you drink, don't drive." When the question of substitute addictions for alcohol was discussed, it was doubted whether pharmacologists would ever succeed in producing a harmless drug which could replace alcohol by producing that feeling of self-transcendance some persons apparently need. There appeared to be a number of routes to alcoholism—one person might seek a mystical experience, another a relief from isolation (our herd-approval-seeking society was blamed for much of this), a third oblivion from guilt feelings. The leader of the seminar pointed out that whereas nobody thought that a little tuberculosis or venereal disease was good for one, folklore said that small amounts of alcohol were good for health. Hence the difficulty of getting the public to cooperate in public health campaigns or even to accept the results of research, if the latter conflict with the folklore.

Tissue Culture of Leishmania Donovani.—The School of Hygiene of the University of Toronto may appear a peculiar place to develop a new method of tissue culture of a tropical parasite. The anomaly is explained by the great interest of this school in tissue culture techniques. Leishmania donovani, the cause of visceral leishmaniasis, has proved difficult to grow on tissue cultures for diagnostic work, but Belle (*Canad. M. A. J.* 79:726, 1958) succeeded by using human epithelial cells from amnion trypsinized to liberate the epithelium, grown on nutrient medium, inoculated with cultures of L. donovani grown on Tobie's medium, and incubated. The parasites began to multiply within 48 hours, and continued to grow in culture even after five serial transfers. The author found that the elongated leptomonads multiplied by longitudinal fission, and some became pear-shaped and aflagellate, subsequently undergoing change to ovoid Leishman bodies.

Fluoridation of Water.—Physicians sometimes lose good causes because they will not stand up and fight. Dr. Sturgeon, health officer to an Ontario district (*Canad. J. Pub. Health* 49:425, 1958), told how physicians joined with dentists to obtain the favorable result of a plebiscite taken in the little town of Thorold to determine whether the town should continue to fluoridate its water supply. Led by the local chiropractor, a so-called citizens' committee, composed mainly of out-of-town members and a few religious cranks, had begun an intensive canvass to abolish fluoridation, when the local health forces stepped into the field with a door-to-door canvass by all available nurses, paid advertisements in local papers, public addresses, a total telephone canvass, and talks to students. The vote in favor of fluoridation was 1,359 to 756, and the most important single contribution to success is said to have been the widely distributed letter signed by all the physicians and dentists in the area. Persons with no convictions about the matter often said that the advice of their physician or dentist had outweighed for them the arguments of the opposition. Moreover the widely publicized statement of the American Medical Association on fluoridation did much to counteract the pseudo-scientific material put out by the opposition. Special

credit should go to one physican who persuaded all his colleagues to put their signatures to the letter which made up the minds of the waverers.

American Academy of Neurological Surgery.—At the meeting of the American Academy of Neurological Surgery in Toronto, in November, T. P. Morley of Toronto said that most cerebral tumor tissue was inherently capable of easier growth than normal adult tissue in culture, but the speed of growth was not related to the degree of anaplasia, and occasionally normal tissue proliferated just as well as the tumor cells. W. J. Horsey of Toronto had inflicted posterior hypothalamic lesions on cats, and used protein-bound iodine (PBI) levels to study thyroid activity afterwards. The PBI levels rose in some cases, though no endocrine changes were seen at autopsy. Presumably there was a disorder of thyroid-stimulating hormone (TSH) secretion. C. Ezrin of Toronto described evidence that there were four normal anterior pituitary cell types, with different staining properties on iron-PAS staining. The alpha, orange-staining cell seemed related to growth hormone and prolactin secretion. The beta, dark-red-staining cell was probably related to a storage form of ACTH and TSH, while the delta cell, staining deep blue, was related to the storage form of luteinizing hormone (LH) and follicle-stimulating hormone (FSH). There was a rather doubtful gamma cell which might contain actively secretory forms of ACTH, TSH, FSH, and LH. In prolonged illness, the delta cells became scarcer in association with a failure of gonadotropic function.

J. W. Scott of Toronto had studied the question of ureteral reflux in dogs, recording bladder and ureteral pressures during increasing bladder distention per urethram. At about 90 mm. Hg pressure in the bladder, urine secretion stopped. At lower levels, intraureteral pressures rose parallel to intravesical pressure, but reflux did not occur. The inference is that in paraplegics it is important to prevent high intravesical pressures from developing. C. G. Drake of London, Ontario, had repaired the facial nerve in three patients by using a graft from the lateral femoral cutaneous nerve of the thigh carried through the posterior fossa. Some return of facial function had occurred. W. M. Lougheed of Toronto had devised a method of introducing blood into the subarachnoid space of dogs through a catheter inserted via a bur hole in the roof of the nose, and was surprised to find that symptoms developed in only 3 of 10 dogs so injected.

S. Birse of Toronto had examined the brains of 19 patients who died after rupture of a berry aneurysm in the anterior cerebral-anterior communicating area. The outstanding finding was that of extensive areas of cerebral softening often detectable only on histological examination, and not at all related to the extent of the subarachnoid hematoma. C. Bertrand of Montreal demonstrated his apparatus for producing needle electrode lesions in the globus pallidus. Lesions 12 mm. in diameter gave durable results as regards reduction of rigidity and tremor in patients with paralysis agitans. To be effective in choreoathetosis, the lesion must be carried further back and involve the corticospinal tract. Murray Falconer of London, England, drew attention to the common association of temporal lobe epilepsy with small focal lesions not detectable even at operation. He had collected 23 cases in which the pathologist had later demonstrated 13 tumors, 2 vascular malformations, 5 cortical scars, and 2 cortical infarcts. Operation had given good results in 21 patients, with complete cure in 14.

INDIA

Determination of Body Fat.—Sen and Banerjee (*Indian Journal of Medical Research*, vol. 46, July, 1958) determined the body fat of 16 men and 9 women by using different methods and compared the results. In the first method, body fat was calculated from the specific gravity of the body determined by the water displacement method according to the formula of Rathbun and Pace. In the second method it was calculated from the density of the body using the formula of Keys and Brozek. The skin fold measurements were taken at different sites by means of calipers over the abdomen, chest, back, and right arm. A high degree of correlation existed between the specific gravity of the body as measured and that calculated from the different skinfold measurements. Thus the skinfold measurements may be used advantageously in place of measurement of the specific gravity of the body by the cumbersome water displacement method. The average fat content of the body calculated from the specific gravity of the body using the first method was 11% of the body weight, while the reading obtained by the second method was 11.3%.

Vaginal Cytology and Uterine Bleeding.—S. J. Kripalani (*Journal of the Association of Medical Women in India*, vol. 46, August, 1958) stated that an abnormality in secretion of hormones is responsible for dysfunctional uterine bleeding. Changes in vaginal smears can indicate the lack or excess of ovarian endocrine functions and the effect of therapeutic hormones. These smears are also helpful in distinguishing dysfunctional bleeding from other causes of uterine bleeding such as abortion or malignancy. The vaginal smears for this purpose should be studied every third or fourth day during the menstrual cycle. The author thus studied 30 women with a clinical diagnosis of functional bleeding. The age of these patients varied from 16 to 45 years; 25 were married, 2 were widows, and 3 were single. Of the married women 11 were nulliparous. The

duration of the disease was on an average 2.4 years. Thirteen had prolonged menstrual periods after periods of amenorrhea; 10 had prolonged periods at short intervals of 6 to 18 days; 5 had excessive bleeding at regular intervals of 26 to 30 days; and 2 had almost continuous bleeding with occasional and irregular cessation. Fourteen patients were studied for three or four cycles regularly and showed two main types of curves, 4 showing hyperestrogenic and 10 showing hypoestrogenic curves. Thus the output of estrogen was lower than normal in 10 of these 14 patients with bleeding. In 5 of the 10 patients with hypoestrogenic curves, endometrial biopsy specimens revealed endometrial proliferation with dilated glands in 2, endometrial proliferation without dilated glands in 1, mixed endometrium indicating irregular ripening in 1, and early secretory changes after the patient had been treated with progesterone in 1. A nonhyperplastic proliferative endometrium or a poorly developed secretory phase indicates subnormal ovarian activity and thus the findings of endometrial biopsy specimens and vaginal smears corresponded in these patients.

From the point of view of treatment, patients with functional uterine bleeding were divided into those with hyperestrogenic and those with hypoestrogenic curves. In two patients with hyperestrogenic curves treated with estrogens, bleeding stopped temporarily with recurrence of irregular bleeding, while the cornification percentage showed a further rise but the clinical symptoms persisted. One patient with a hyperestrogenic curve was treated with progesterone but the intensity of bleeding increased and the treatment was stopped. Two patients with the same type of curve were treated with testosterone during the bleeding phase. Good results were seen in both and normal flow at regular intervals was seen during the next three or four cycles. Vaginal smears in the following cycles indicated anovulatory cycles. Two patients with hypoestrogenic curves responded well to treatment with estrogens. Results with progesterone in this type of curve were unsatisfactory. One patient with hypoestrogenic curve was treated with testosterone. An immediate hemostatic effect was produced but the delayed effect was a prolongation of the intermenstrual periods to 40 or more days. The next two menstrual periods were anovulatory and there was hardly any difference in the cornification percentage. Testosterone should thus not be given to patients with hypoestrogenic curves.

Experimental Cataract.—K. Bagchi (*Journal of the Indian Medical Association*, vol. 31, Oct. 1, 1958) stated that the incidence of senile cataract was much higher and its age of onset much lower in countries where protein malnutrition was prevalent. The high incidence and early age of occurrence in India has been explained as possibly due to the effect of sunlight or ultraviolet irradiation. Probably protein malnutrition, which is also widely prevalent here, causes early lens changes. A further insult then in the form of ultraviolet light may precipitate the development of a clinical cataract. To investigate the effect of general protein malnutrition on the lens, the author fed young pigs diets containing 4.5, 6.5, and 10% of protein. Their body weights were recorded and their lenses examined for sulfydryl and glutathione which are decreased in all forms of cataract and precataract conditions. The lens was also examined histologically. The growth rate in all the three groups of animals was found to be much lower than that of control animals that were given a 20% protein diet. The pigs on the lowest protein level showed no increase in body weight. A mature cataract was seen in these animals after about three months. The glutathione and protein-bound sulfydryl contents of the lens (calculated by noting the difference between the total sulfydryl and the glutathione content) were lower as compared to normal. As a result of this reduction, probably the enzymatic activity in the lens is reduced affecting the essential metabolism and leading to lenticular damage.

The biochemical and histological features of these cataractous lenses closely resembled those seen in rat lenses made cataractous by making them deficient in methionine. The pathogenesis of the protein deficiency cataract in pigs may therefore be similar. Thus, although evidence of production of cataract due to protein malnutrition was obtained, no mention of its development in human beings suffering from protein malnutrition has appeared so far in literature. Probably in countries such as India, where protein malnutrition is widespread and cataracts appear at an early age, biochemical changes are produced in the lens in the growing phase as a result of protein deficiency which are not diagnosed by ordinary ophthalmologic examination but may be detected by examination with a slit-lamp microscope. These damaged lenses then develop cataract when further subjected to such factors as ultraviolet light or deficiency of methionine.

Meprobamate and Mental Disease.—Satya and Bhaskaran (*Journal of the Indian Medical Association*, vol. 31, Oct. 1, 1958) treated 27 patients who had various mental disorders with meprobamate given orally, each tablet containing 400 mg. The conditions for which these patients were treated were schizophrenia, catatonic excitement, mania, behavior disorders, anxiety states, alcoholism, and premenstrual tension. The ages of the patients were 19 to 49 years. They were studied for 10 months. Treatment was started with an initial dose of one tablet three times a day. This was gradually increased to six or more tablets a day, the duration of treatment varying from 21 to 181 days. The results

were assessed by noting the improvement in the mental condition and reports from occupational therapists, nurses, and social workers.

Results were unsatisfactory in the two patients with catatonic excitement although they were quieter. Fifteen patients with chronic schizophrenia were included in the trial, the duration of illness varying from 3 to 17 years. All these patients had previously undergone a full course of insulin shock, electro-shock, and reserpine or chlorpromazine with no significant benefit. Only three of these improved on treatment with meprobamate. The drug led to sedation without sleepiness and more cooperative behavior but the presenting symptoms did not disappear. Of five patients with manic reaction, one improved but the others showed no change. The drug was of no use in one patient with behavior disorder and mental deficiency. Four patients with psychoneuroses showed marked improvement. Six patients with chronic psychoses who had had no treatment for a long time were given 1.2 Gm. of the drug in a single dose to determine its hypnotic effect. One felt drowsy two hours after the drug was given but was still responsive to verbal stimulation, the effect lasting for about six hours. Others did not feel drowsy but looked more relaxed. Six patients were subjected to routine electroencephalography which was repeated three hours after 1.2 Gm. of the drug was given by mouth. Two days later electroencephalograms were again made three hours after the administration of 75 mg. of chlorpromazine by mouth. No change in the routine record was seen in any patient nor did the brain potentials show the patterns of normal sleep.

SWEDEN

Plea for a Poison Control Center.—Four articles in *Svenska läkartidningen* for Oct. 24 draw attention to Sweden's need for a poison control center. To demonstrate this need, an inventory was taken of the various chemical-technical preparations stocked in 10 homes of physicians and druggists. The 230 such preparations listed could be classified in five groups according to their functions and composition. The preparations in the first group, such as turpentine, were straightforward enough insofar as accurate information about them could be obtained in any standard textbook of toxicology; but many of the other preparations had proprietary names giving no clue to their composition, hence their toxicity when children have swallowed them and it is desired to use the appropriate antidote. In such cases the services of a poison control center possessing all the necessary data would be invaluable to the physician. At the Sachsska Children's Hospital in Stockholm, Dr. Allan Alvin analyzed the 1,026 cases treated by gastric lavage in the period 1953 to 1957. Tobacco was responsible for 44% of these cases and drugs for 24%. Next were chemical-technical preparations (23%), poisonous plants (4%), and the indelible pencil (5%). This pencil contains the relatively nontoxic gentian violet. Pending the creation of a poison control center, Alvin would like to see published an illustrated toxicological botanical map to serve as a guide to the physician called on to treat a case of poisoning by some plant.

Alcoholic Psychoses.—Nilsson and Frey (*Svenska läkartidningen*, Oct. 24, 1958) observed 476 men with delirium tremens at various periods between 1946 and 1957, during which time there was a continuous increase in the incidence of such admissions to the Lillehagens Mental Hospital. The removal of certain restrictions on the sale of alcohol in 1955 must be held responsible for much of this rise, the admission rate for such cases being many times higher in 1957 than in 1946. No favorable effects from cortisone or reserpine were observed, but excellent results were obtained with electroplexy treatment of auditory hallucinations that had lasted over a week. Much was achieved with antibiotics in combating the pulmonary complications, the mortality from which was thus appreciably reduced.

Myocardial Infarction.—If we knew what predisposes to myocardial infarction its prevention and treatment could be greatly facilitated. Forssman and Lindegard (*Svenska läkartidningen*, Oct. 24, 1958) studied 66 men who suffered from this disease. They had survived the infarct by at least two months and most of them by a year. None was older than 55 years, and most were between 45 and 55. For each patient a healthy control of the same age and sex was chosen at random. Among the many criteria by means of which patient and healthy control could be compared were leadership in occupation, mortality from arteriosclerosis under the age of 70 among the parents, height and weight measurements, explosive and moody temperaments, serum cholesterol levels, and the excretion of steroids in the urine. With regard to the two last criteria, it was found that both patients and controls could be grouped in subgroups according as the serum cholesterol level and the excretion of steroids in the urine was high or low. On the whole the patients were characterized by a high serum cholesterol level and a low steroid excretion as compared with the controls. Because so many criteria were invoked in this study, it was difficult to evolve any mathematical formula from them, and the prophylactic measures to be advocated on the base of this material were only tentative.

Arthrosis of Knee.—At an orthopedic hospital in Norrköping, Dr. S. Nilsson (*Svenska läkartidningen*, Oct. 31, 1958) has since 1957 injected hydrocortisone acetate or prednisolone acetate into the knee

joint of 48 patients suffering from arthrosis deformans of the knee. Their ages ranged from 40 to 82 (average 62) years. Most of them had previously undergone x-ray treatment six months or more earlier usually with some brief subjective improvement. The disease had lasted 1 to 15 (average 4) years. Under strict asepsis the punctures were made from the side through the suprapatellar bursa, any fluid present being aspirated before the injection was made. No relief of pain was effected during or after the injection by injecting a local anesthetic as practiced in about half the patients. Fifteen complained of transient, relatively intense pain for a few hours after the injections which were given according to two different patterns, either with five after-intervals of four days or with three after-intervals of seven days. With only 10 exceptions, improvement was effected, and this was so great that it amounted to complete disappearance of pain in 14. The results were best in the slight and early cases and in such as were associated with hydrops of the knee. The duration of improvement was also longer for the light than for the severe cases. No great difference could be detected between the action of the hydrocortisone and that of the prednisolone. Both helped to correct extensor defects of the knee in conjunction with prescribed exercises.

UNITED KINGDOM

Neoplasms After Irradiation.—The *British Medical Journal* of Oct. 18 contains three articles on thyroid neoplasms after irradiation. The first is by the staffs of the departments of pharmacology and therapeutics, pathology, and surgery, University of Sheffield, and the Sheffield National Center for Radiotherapy. They reported a series of nine patients with thyroid neoplasms. In all of them the thyroid had been exposed several years previously to ionizing radiation. In seven, indisputable histological evidence of carcinoma of the thyroid was present, and in six, infiltration outside the gland or metastases had occurred. In six the thyroid had been incidentally exposed to irradiation in infancy or childhood during the treatment of cutaneous lesions by radium or x-ray. In them the dose to the thyroid varied from 130 to 2,700 r, and the latent period from 5 to 18 years. The carcinoma developed in the part of the thyroid exposed to the greatest irradiation. The seventh patient was irradiated for the treatment of thyrotoxicosis when she was 26 years old and had an anaplastic carcinoma 37 years later. In two patients a nodular enlargement of the thyroid developed after irradiation. Histologically, hyperplastic adenomatous areas and mitotic figures were seen, but in the absence of local invasion and metastases, the histological features alone did not justify a diagnosis of carcinoma. They were regarded as premalignant conditions. The authors concluded that exposure in childhood predisposes to the appearance of thyroid neoplasms. The association after irradiation in adult life is less certain.

In the second article Dr. A. W. Goolden said that there is little evidence to suggest that the adult thyroid is susceptible to radiation cancer. The development of carcinoma of the thyroid in three patients after irradiation of the neck was reported. Two of the patients received irradiation in adult life. It was probable that the tumors in these three patients were induced by radiation, but it would be necessary to carry out a large-scale survey to find out whether irradiation of the thyroid gland in adult life increased the incidence of thyroid cancer.

An editorial on this subject stated that conclusions based on previous experience with thyroid irradiation must refer to external irradiation by x-rays or radium, but, since the latent period for the development of carcinoma after irradiation in adults is probably at least 20 years, no conclusions can yet be based on any series of patients who have received radioactive iodine, since this isotope has been in clinical use for only about 16 years. Theoretically, owing to the wide variation in the radiation dosage from the absorbed isotope sustained by the thyroid cells at different points, it is certain that some cells surviving damage will have been irradiated with a dose which in other tissues would lead to tumor formation. The risk of the late development of carcinoma in children in particular makes it justifiable only in exceptional circumstances to use radioactive iodine even for diagnostic purposes, or to use x-rays or radium in the neighborhood of the thyroid in the treatment of simple conditions such as thymic enlargement, nevi, and keloid scars. In later adult life the risk of carcinoma is probably of less importance, but further study of it is needed.

Nuffield Bounty.—In the first 15 years of its existence the Nuffield Foundation has given away about $24,000,000. Of this, $18,000,000 has been spent in the United Kingdom and $5,600,000 in the Commonwealth. Science and technology have received $5,000,000, medicine $4,200,000, care of old people and research into aging $2,800,000, and social research and education $3,500,000.

Phonocardiography and Electrocardiography of the Fetus.—Fetal heart rate, rhythm, and waveform were studied by phonocardiography and electrocardiography from the surface of the mother's abdomen by Smyth and Farrow (*Brit. M. J.* 2:1005, 1958). For phonocardiography, which is the most suitable method for recording heart rate and rhythm and for estimating the systolic and diastolic time intervals, the microphone is applied to the point on

the abdomen where the heart is best heard. It is not unduly affected by extraneous noises but is by the mother's speech or movement, or by borborygmi. The principal uses of phonocardiography are to monitor the fetal heart and to check regularity of rhythm and rate after version, the giving of drugs such as oxytocin, or surgical induction of labor, and during the induction of anesthesia or forceps delivery. It is also of use in the diagnosis of fetal distress.

Electrocardiography is done by firmly placing on the linea alba the two electrodes, which form the two feet of a metal box containing the preamplifier. A metal belt for the indifferent electrode is placed round the mother's waist between the uterine fundus and the heart. Owing to extraneous disturbances the records of P and T waves are difficult to distinguish with certainty, but the QRS complex can be recorded faithfully in amplitude and duration. If clinical requirements necessitate a full fetal electrocardiogram with P and T waves, as in fetal distress, or before emergency cesarean section, then intrauterine electrodes are passed through the cervical canal, preferably after rupturing the membranes, and their positions ascertained radiographically if necessary. The principal uses of electrocardiography are for the differential diagnosis of pregnancy and multiple pregnancy from tumors; for evidence of fetal life in cases of threatened abortion; for differentiation of breech from cephalic presentation; and to demonstrate the presence of fetal cardiac abnormalities, such as myocardial failure, impeded circulation, and fibrillation. The electrocardiographic diagnosis of heart block normally requires intrauterine electrodes. Records were obtained during electrocardiography which were thought to be due to discharges from the fetal brain. Further improvements in technique are needed before these can be interpreted. They may be artifacts.

"On Call to a Nation".—The British Broadcasting Corporation celebrated the 10th anniversary of the introduction of the National Health Service by televising a documentary film entitled "On Call to a Nation." The film, lasting for 75 minutes, was the longest documentary ever made by the B. B. C. There were no professional actors in it. All the parts were taken by physicians, dentists, and medical personnel working in their usual surroundings in the hospital clinic or in general practice. The film was not intended to show the inner working of the Health Service but rather to show physicians in action and to obtain their views of the Service. Fifty-seven physicians appeared and 25 of them spoke. They included those in urban and rural practice, those with large and small patient lists, those in group practice, and hospital specialists. As payment in general practice is on a per capita basis, it is significant that an urban general practitioner with a large list said that he approved of the Service, while one in a rural area with few patients, who had to travel great distances to see them, did not. Other practitioners and specialists also had various reservations and criticisms to make. A consultant dictating letters at the end of an outpatient session gave his views. Another pointed out the cost of the Health Service to the nation and the public's responsibility for financing it. A pricing bureau was shown dealing with millions of prescriptions to highlight the cost of drugs. The need for increased capital expenditure was emphasized by views of old hospitals and temporary buildings that had long outlived their usefulness. General practitioners were shown seeing their patients. Professional bodies had been consulted, but the planning and direction of the film were done independently.

Poliovirus in Children Under Five Years of Age.—An investigation by the Public Health Laboratory Service showed that about 0.2% of children under 5 years of age are symptomless carriers of poliovirus, the figure rising to 2.5% at the height of an epidemic (*Monthly Bulletin Public Health Laboratory Service*, Oct., 1958, p. 231). The real figure is probably higher than this, as the method of isolating the virus was not entirely satisfactory. The results were based on a survey of 21 areas, both urban and rural, in England and Wales. This carrier rate was found to follow the seasonal curve of poliomyelitis incidence fairly closely at first, but fell off more slowly than that of the reported cases. No clearcut relation between carrier rate and incidence of reported poliomyelitis was found, although there was a rough correlation between the two. The areas studied fell into two groups, with high and low carrier rates respectively. In those with the high carrier rates there were about 50 carriers for every reported case and in the low group the corresponding ratio was about 15:1.

Rockefeller Grant.—The Council of the Royal Society of Medicine announced that the Rockefeller Foundation had offered a grant of $67,370 to the Society for the support of its library over the next five years, while endowments are being sought to ensure its service and maintenance. The library contains 400,000 volumes and nearly 2,000 current periodicals. It is used by more than 60,000 readers annually.

Nobel Prize Winner.—Dr. F. Sanger, head of the Medical Research Council's biochemistry research unit at Cambridge, was awarded the Nobel Prize for Chemistry. After 10 years' research he identified the amino acid constituents of insulin. Four years ago he was made a Fellow of the Royal Society and of King's College, Cambridge.

CORRESPONDENCE

ORGAN PLAYING

To the Editor:—Although the Leisure Corner item in the Oct. 11, 1958, issue of THE JOURNAL, entitled "Playing the Modern Organ" is interesting, two points should be clarified. In the early so-called water organs, the water was not used to create the air pressure to make the pipes speak, but rather was used in the manner of a diving bell to keep the air pressure constant and thus to keep the tone of the pipe in pitch. In the first paragraph of the article, it is stated that the organ is easy to play, and later, that the modern organ is probably the easiest of all instruments to play. If by organ we mean the instrument on which most of the pieces written for organ can be played, it would have to have two or more manuals and 32 pedals. This instrument is not easy to play. Some organ teachers require six years study on the piano before they will permit a student to start on the organ. A person, by reading the Leisure Corner article, might be misled into believing he could play serious organ music without a lot of hard work, which is not true.

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MAMMARY CARCINOMA

To the Editor:—I am disturbed by the erroneous impression given by the editorial on mammary carcinoma in THE JOURNAL (168:1228 [Nov. 1] 1958). It would appear from the editorial that the only type of endocrine therapy worth while is surgical removal of either the ovaries, the adrenals, or the pituitary. I believe that this is not only a fallacious impression but is not in the best interest of patients. While the administration of endocrine preparations is mentioned, the editorial states only that the drugs are especially useful in getting patients in better condition for ovariectomy or adrenalectomy and in treating patients with cerebral metastases, hypercalcemia, and lymphedema. I am afraid that many people will be deprived of years of useful remission from hormonal therapy if such treatment is limited to these indications. I agree that ablative therapy is an impressive *tour de force* to the patient, but one cannot ignore the fact that such procedures still work after hormonal preparations have been given and also that, in general, these procedures should not be performed just anywhere by anyone. Adrenalectomy may be technically easier than hypophysectomy, as was pointed out, but it is still an extensive major procedure and the patient is left living a precarious life forever after.

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MEDICAL FILM REVIEWS

Machine Mimics Man: The Artificial Kidney: 16 mm., color, sound, showing time 26 minutes. Prepared by Willem J. Kolff, M.D., Cleveland, and George E. Schreiner, M.D., Washington, D. C. Produced in 1958 by Mervin LaRue, Inc., Chicago, for and procurable on loan from Travenol Laboratories, Inc., Division of Baxter Laboratories, Morton Grove, Ill.

By animation and clinical photography this film shows, step by step, the ease of setting up the Travenol Twin-Coil Kidney and the speed with which hemodialysis is available to the patient. Also reviewed are normal kidney function, the basic principles of hemodialysis, and its role in renal insufficiencies and certain systemic poisonings. The important thing about this film is its instructive mechanical aspects for anyone who might be interested in applying this form of therapy. The procedure has gradually been simplified until the Travenol Twin-Coil Kidney seems to offer the most efficient means of hemodialysis available at the present time. The basic principles of hemodialysis and its therapeutic possibilities, in patients with renal insufficiency, especially that which follows systemic poisoning, and other difficulties which call for temporary dialysis, are simplified for quick comprehension. The only criticism to be leveled at this excellent film would be that the explanation of procedure makes it seem almost too simple and might delude some persons into thinking it foolproof. This, of course, is far from the truth, and anyone applying this more or less portable unit should have a thorough basic understanding of the entire subject. The film is highly recommended for showing widely as an educational feature and should be a "must" for any and all newcomers to the field of hemodialysis who are contemplating use of the Travenol Twin-Coil Kidney.

MEDICAL LITERATURE ABSTRACTS

INTERNAL MEDICINE

A Reversible Nephrotic Syndrome Associated with Congestive Heart Failure. W. R. Burack, J. Pryce and J. F. Goodwin. Circulation **18**:562-571 (Oct.) 1958 [New York].

A nephrotic syndrome is an unusual and puzzling complication of chronic heart failure. The authors report 4 patients in whom severe proteinuria, hypoproteinemia, massive edema, hypercholesterolemia, and a strikingly abnormal plasma electrophoretic pattern developed in the course of congestive heart failure. The blood urea level was normal or only slightly elevated, and the urinary sediment was normal. Three of the 4 patients recovered from the nephrotic syndrome over a period of 9 months on a regimen of digitalis, low-salt and high-protein diet, and regular, weekly, intramuscular administration of mercurial diuretics. Aminophylline given intravenously just prior to the mercurial was found to enhance the diuretic response.

Reference is made to the little understood but common phenomenon of proteinuria in heart failure. The possible relationship of the proteinuria to the occasional case of nephrotic syndrome is discussed. It is concluded that the nephrotic syndrome occurring in chronic heart failure is not caused by mercurial diuretics and is not in itself a contraindication to their continued use.

The Frequency of Postprimary Pulmonary Tuberculosis According to Pulmonary Arterial Pressure. S.-B. Mattson. Am. Rev. Tuberc. **78**:536-546 (Oct.) 1958 [New York].

The author points out that it has been debated for more than a century whether or not certain cardiac valvular defects confer increased resistance to pulmonary tuberculosis. No uniform opinion has been reached. This report describes another attempt to elucidate the question of pulmonary tuberculosis in organic heart disease. The case material for the study was obtained from 2 cardiac clinics in Stockholm, which accept patients from all of Sweden. All cases of congenital cardiac anomaly or of mitral disease in which heart catheterization was performed during the years 1948-1956 were reviewed. The series was confined to persons more than 15 years old. Most of these 413 persons had been referred to the clinics with a view to surgical relief of the cardiac defect. The patients were classified according to the pressure in the pulmonary artery. This pressure was high in 261 patients, normal in 91, and low in 61. Postprimary pulmonary tuberculosis was present in 1% of the hypertensive patients, in 3% of the normotensive group, and in 13% of the hypotensive group. The difference in tuberculosis frequency (10%) between the normotensive and the hypotensive patients was statistically significant. The corresponding difference (12%) between the hypertensive group and the hypotensive group was likewise significant.

Silicotuberculosis: Results of Medical and Combined Medical-Surgical Therapy. C. S. Morrow and M. Kantor. Am. Rev. Tuberc. **78**:524-535 (Oct.) 1958 [New York].

The patients studied were hard-coal miners. All were admitted to the hospital between Sept. 10, 1952, and Dec. 1, 1956, and had bacteriological confirmation of the diagnosis of pulmonary tuberculosis. Several sputum specimens contained tubercle bacilli on microscopy and/or culture. All had roentgenographic evidence of silicotuberculosis, had had no previous course of chemotherapy, and were treated continuously with antituberculous drugs for at least a 6-month period in the hospital. Twenty-five patients participated in this study, and all but one satisfied the criteria; in the one exception, the chemotherapy had been interrupted for a relatively short period of time. All but 6 of the patients were between 50 and 70 years of age, and these patients had worked in the mines for about 30 years.

Nineteen of the patients received chemotherapy alone, chiefly streptomycin and isoniazid; the other 6 with unilateral cavitary disease were subjected, in addition, to various thoracic surgical procedures. The results of chemotherapy alone, from the standpoint of cavity closure along with reversal of infectiousness, were poor as compared with those for patients with nonsilicotic tuberculosis. The results of chemotherapy and surgery in the 6 patients were good, particularly with the resectional procedures. If chemotherapy alone is to play a significant role in silicotuberculosis, it would appear advisable to

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regard conglomerate disease in its initial stages as tuberculous, in the presence of a positive tuberculin test, and to treat it as such if only to prevent further conglomeration.

Local Reactivation of the Primary Tuberculous Focus in the Lung. J. Snijder and T. Vossenaar. Am. Rev. Tuberc. 78:547-564 (Oct.) 1958 [New York].

The primary pulmonary focus has a tendency to a stereotyped course, complications due to inflammation in the regional lymph nodes being fairly frequent, but the pulmonary focus usually subsides and often becomes calcified. In the rare cases in which the primary focus is progressive, 2 types of local extensions occur. 1. Extensions occur before the focus has subsided (type 1). 2. The pulmonary focus becomes reactivated when the primary complex has been quiet for years (often containing calcium), and the patient meanwhile has been considered healthy (type 2). At the "Berg en Bosch" Sanatorium in Bilthoven, The Netherlands, cases of type 2 reactivation were collected. Their rarity is demonstrated by the fact that among 4,554 patients who were discharged from "Berg en Bosch" there were 12 with a local reactivation of an already subsided pulmonary focus; thus, the frequency was about 0.25%. Seven of these patients were less than 15 years old, and the remaining 5 ranged from 15 to 27 years of age. The authors now have under observation a 14-year-old girl with the same condition; thus, a total of 13 instances have been studied.

In 12 of 13 cases the diagnosis could be based on accurate data: in 8 patients the primary complex in its active stage had been recorded on chest films, and in 4 patients a partly calcified primary complex, which had subsided before the onset of the present disease, could be demonstrated from the roentgenograms. In the remaining case the diagnosis was practically certain. Complaints and symptoms were hemoptysis, high temperature accompanied by general malaise, cough, expectoration, fatigue, weakness, and loss of weight. Acceleration of the erythrocyte sedimentation rate and changes in the differential leukocyte count were also observed. Not every patient had all these symptoms, but tubercle bacilli were present in the sputum almost without exception. Depending on the nature and the extent of the liquefaction in the focus, tubercle bacilli in the sputum varied from large numbers seen on microscopy to an occasional one obtained only by culture. The causes of reactivation could not be determined from either the history or the clinical data.

Roentgenographically, the fairly voluminous foci were usually sharply demarcated from the surrounding tissue. The size varied from that of a cherry to that of a chestnut, but one focus was as large as a hen's egg. Nearly all the foci (11 of 13) contained calcium. All foci but one contained a cavity. Except in one case, the cavity was fairly small as compared with the size of the focus. A striking feature was the eccentric position of the cavity, which was invariably situated opposite the calcium deposits. The local extension was accompanied by disseminations, which in the majority of cases were limited to small foci in the immediate surroundings of the large focus. Nine of the foci were localized subpleurally.

The authors regard local reactivation of an initially subsided primary tuberculous pulmonary focus as an indication for a pulmonary resection. The treatment was nonsurgical in only 2 of the patients. In the 11 patients who were operated on, the postoperative course was uneventful, and a satisfactory reexpansion was obtained. All the patients remained in excellent condition after discharge from the sanatorium. Examination of the resected foci showed that they were composed of a small, older portion and a larger, more recent area. The older part consisted of a largely calcified caseous focus. Mycobacterium tuberculosis was exclusively found in the recent area, in the liquefied caseum. In 3 cases, in which the caseous material of the focus was cultured for tubercle bacilli, viable tubercle bacilli were present.

The Effectiveness of Long-Term Treatment of Malignant Hypertension. H. P. Dustan, R. E. Schneckloth, A. C. Corcoran and I. H. Page. Circulation 18:644-651 (Oct.) 1958 [New York].

A majority of patients with hypertension die prematurely, not of hypertension or hypertensive vascular disease as such, but of complications of hypertensive and coronary heart disease, cerebrovascular damage, or some other arterial (not arteriolar) catastrophe. Potent antihypertensive drugs have been in use for 7 or 8 years, but with a lack of information on the relation between the cause of death and the extent of arteriolar damage it is impossible to assess therapeutic gains in terms of prolongation of life or prevention of complications. The situation is quite different in the malignant (accelerated) phase of essential hypertension. The course of this hypertensive syndrome is well characterized, predictable, and relatively brief, with survival of only 10 to 20% of patients for one year. Death is caused primarily by hypertensive arteriolar vascular damage. This is commonly expressed by malignant nephrosclerosis with rapidly progressive renal failure, by intracerebral hematoma, and not infrequently by uncontrollable cardiac failure.

Surveying the courses of 84 patients with malignant hypertension who received treatment with potent antihypertensive agents during the past 7 years, the authors found that 70% survived 1 year of observation; 50%, 3 years; 33%, 5 years; and 26%, 6 years. These survival rates represent substantial

therapeutic gains over survival rates in the untreated series of Keith, Wagener, and Barker. The first-year survival rate was weighted by the untoward complication of hexamethonium pneumonitis, and current survival is greater. Other causes of death were rapidly or slowly progressive renal failure and complications of atherosclerosis. The rapidly progressive renal failure was usually associated with poor control of blood pressure. It seemed merely an attenuation of the usual course of malignant hypertension. The syndrome of delayed or slowly progressive renal failure was associated with diffuse occlusive fibrous intimal hyperplasia of major renal arteries. Among the complications of atherosclerosis, cerebral hemorrhage was the most common and was associated with poor control of blood pressure level, while myocardial infarction, the next most common, was not.

It may be that the coronary arteries, like the renal, are subject to progressive occlusive disease in some patients with treated malignant hypertension. It is not clear whether this process represents a continuation in vessels larger than arterioles of a basic vascular disease or a delayed response on the part of the arteries to preexisting severe hypertension. Survival was better in patients who were treated before malignant hypertension had caused extensive vascular damage. Patients who presented themselves for treatment with evidences of severe renal damage generally did not survive for long periods. However, several such have maintained active lives for many months and years. Hence, treatment should be withheld only in the most desperate circumstances.

Temporary Collapse in the Treatment of Pulmonary Tuberculosis. F. T. Rogue. Dis. Chest **34**:404-412 (Oct.) 1958 [Chicago].

Rest has generally been accepted as fundamental in the treatment of pulmonary tuberculosis. Tuberculosis sanatoriums were established to provide a haven of rest for those afflicted with the disease as well as to segregate them from the general population. Temporary collapse measures, namely, artificial pneumothorax, pneumoperitoneum, and phrenic nerve paralysis, basically are attempts to secure rest by so-called "splint" or "selective collapse" of diseased lungs. The author reports on the changing status of these temporary collapse measures in the past 10 years at Fitzsimons Army Hospital in Denver and gives his own views based on experiences since 1933. He regards artificial pneumothorax and phrenic nerve paralysis as obsolete procedures. If after adequate use of antituberculous drugs cavitary lesions constitute caseonodular residuals that involve the threat of recurrence, surgical excision is the procedure of choice. Pneumoperitoneum may be used as a last resort in far-advanced cases when, after adequate and prolonged chemotherapy, surgical excision of cavities and/or serious residuals cannot be performed because of serious impairment of pulmonary function. Pneumoperitoneum may be considered also in those rare patients in whom chemotherapy cannot be used because of severe toxicity.

The Effect of Treatment on Mortality Rates in Severe Hypertension: A Comparison of Medical and Surgical Regimens. H. M. Perry Jr. and H. A. Schroeder. A. M. A. Arch. Int. Med. **102**:418-425 (Sept.) 1958 [Chicago].

The mortality rates of 209 patients with severe hypertension, treated orally with such a ganglion blocking agent as hexamethonium chloride and with hydralazine hydrochloride, have been compared with the mortality rates reported in the literature as being associated with other antihypertensive regimens, particularly surgical sympathectomy. The comparison was made difficult by the differing criteria used by various authors in grading the severity of the disease prior to therapy. Because effective antihypertensive drugs have been used for a relatively short period, they could be evaluated only in seriously ill patients with significant and predictable mortality rates during the available observation period. This series of previously untreated nonuremic patients, 23 of whom were Negroes, were divided on the basis of their pretreatment status into 2 groups, according to Smithwick's classification; thus, 79 patients were classified as group 3, and 130 as group 4. Their ages ranged from 27 to 70 years, with an average of 49 years. All the patients were followed for 4 years. Of the 130 patients in group 4, 48 had benign hypertension, and 82 were considered to have malignant hypertension, which was associated with azotemia in 35 without evident cardiac failure or any of the common signs of uremia and 47 were nonazotemic. All 82 patients with malignant hypertension had proteinuria and papilledema; 77 had hemorrhagic and exudative retinitis, while 3 had only hemorrhages and 2 only exudates. Each of the 82 patients had a mean supine diastolic pressure of over 130 mm. Hg.

Therapy with the oral administration of hexamethonium chloride and hydralazine hydrochloride was instituted according to a regimen involving an invariant dose of hydralazine plus a variable dose of the ganglion blocking agent 3 or 6 times a day, with the dose of the latter depending on the level of systolic pressure. During the 4 years after the institution of therapy, the mortality was lower in this series of patients treated with a combination of ganglionic blockade and hydralazine than it was in Smithwick's reported series of surgically sympathectomized patients. If the severity of the cardiovascular disease in the group 4 patients was graded

on the basis of both hypertensive and atherosclerotic processes, the mortality rate of the patients who were medically treated was 43% and that of the patients who were subjected to operation was 48%. In the nonazotemic patients with malignant hypertension, if classification was based only on the hypertensive process, the mortality rate of the patients who were medically treated was 36% and that of the patients who were operated on was 48%. For all groups of nonazotemic patients who survived the first year of medical treatment with adequately controlled diastolic pressure, the mortality rate approximated 10% during the next 3 years. Mortality was related to race, being noticeably higher among Negroes, but was relatively independent of sex, age, and economic status.

Second Field Evaluation of Bivalent Types 4 and 7 Adenovirus Vaccine. M. R. Hilleman, H. H. Greenberg, M. S. Warfield and others. A. M. A. Arch. Int. Med. **102**:428-436 (Sept.) 1958 [Chicago].

A second field evaluation of bivalent types 4 and 7 adenovirus vaccine, prepared by Lederle Laboratories by commercial production procedures, was carried out at Fort Leonard Wood, Mo., during the winter of 1957. The study proved the high degree of efficacy of this vaccine for preventing acute respiratory diseases of different causes in newly recruited soldiers. The incidence of various respiratory diseases was 11.0% among the 2,471 vaccinated subjects and 23.8% among persons of the control group who received a formalin-saline placebo; thus, a reduction of 55% in the attack rates for total respiratory diseases was obtained by the vaccine. The protective effect of the vaccine became evident about 7 days after vaccination. The adenovirus specific attack rates, calculated on the basis of serodiagnostic tests on an approximate 50% sample of cases, were 1.6% in the vaccinated subjects and 16.6% in the control group, and the reduction in cases was 90%. These findings compared favorably with a 98% reduction figure obtained earlier in a study. The complement-fixation test used in this study proved to be a highly reliable diagnostic means of determining whether the respiratory disease was caused by adenovirus even in vaccinated subjects.

Adult civilian groups have shown very low attack rates for adenovirus-caused respiratory disease; therefore, general vaccination of such persons is not justified. There may be a greater need for the vaccine among children and infants. Whether the attack rates in children are sufficiently high to warrant general use of an adenovirus vaccine, what particular types of adenovirus should be included in the vaccine, and whether the vaccine is effective in preventing respiratory diseases caused by adenovirus infection are questions that require further investigation. In taking into consideration the use of adenovirus vaccine in any group of the population, one should bear in mind that this vaccine is ineffective against the common cold.

Production of Hepatic Coma by Carbonic Anhydrase Inhibitors in Patients with Hepatic Cirrhosis. E. Rissel, H. Schnack, N. Stefenelli and F. Wewalka. Schweiz. med. Wchnschr. **88**:946-951 (Sept. 27) 1958 (In German) [Basel, Switzerland].

When ascites develops in patients with decompensated cirrhosis of the liver, the removal of water represents one of the most important problems. Among 85 patients with hepatic cirrhosis who were treated with acetazolamide (Diamox), the authors observed 9 patients who had precomatose or comatose episodes. It was found that the comatose attacks that followed the administration of Diamox corresponded to the "ammoniacal encephalopathy" that develops in patients with hepatic cirrhosis either spontaneously or after the administration of ammonium chloride or cation exchange agents that liberate ammonia, after intestinal hemorrhages, or after high-protein diets. The development of the comatose condition is not dependent on the dose of Diamox. As in spontaneous liver coma, the blood ammonia content showed a noticeable increase in all except one patient in whom Diamox had brought on a comatose state.

Frequently the comatose attacks were reversible, but they may also cause death of the patient. In some patients the coma could be counteracted by the intraperitoneal administration of from 200 to 500 cc. of a 10% solution of glutamate. The administration of potassium prior to Diamox treatment prevented the comatose disturbance in only one patient. In most of these 9 patients Diamox failed to exert a diuretic effect. The administration of Diamox was followed by comatose attacks only in patients with advanced hepatic cirrhosis, such as those in whom coma-like attacks had been elicited by other mechanisms. The prognosis was extremely poor in these patients. All except 2 died within 5 months after the first Diamox-induced comatose attack.

The blood ammonia content was investigated in 12 cirrhotic patients in whom Diamox did not cause coma, and it showed no uniform behavior. Simultaneously existing chronic renal diseases exerted no influence on Diamox tolerance. The large majority of patients with hepatic cirrhosis reacted to doses of 250 mg. of Diamox on 3 successive days, or to 125 mg. of Diamox daily for from 2 to 4 weeks, without showing any coma-like disorders. A hypochloremic coma, such as has been observed after the use of mercurial diuretics, was never observed by the authors. They conclude that, if suitable precautions are taken, Diamox can be used even in decompensated patients with cirrhosis and that it has definite advantages over mercurial diuretics.

Selected Aspects of Acute and Chronic Gouty Arthritis: An Internist's Interpretation of an Orthopaedist's Experiences with Gout and Gouty Arthritis. J. H. Talbott. J. Bone & Joint Surg. 40A:994-1002 (Oct.) 1958 [Boston].

The arthritis clinic at the Buffalo General Hospital is especially interested in gout and gouty arthritis and, because of this special interest, has had an opportunity to consider the varied problems of the patient with acute gouty arthritis as well as the patient with chronic tophaceous gout. There are several features of gout and gouty arthritis of particular interest to the orthopedic surgeon. A presumptive diagnosis of acute gout should be entertained in any unexplained acute inflammation of one or more joints, particularly in an adult male. A family history of gout, renal lithiasis, or other ancillary features may be noted. Most important is a clinical description of the acute attack, which displays the cardinal signs of inflammation and may be associated with pyrexia, leukocytosis, and an elevated sedimentation rate. Confirmation of the diagnosis rests upon a prompt response to a full course of colchicine. The level of serum uric acid is not a reliable diagnostic aid. Roentgenographic evidence in the earlier years of the disease is confined to soft-tissue swelling at the time of the acute attacks.

The cause of the acute attack is not known. The pathogenesis of the underlying metabolic disturbance is associated with an increased formation of uric acid by the body. Diminished destruction and impaired excretion by the kidneys as a cause have not been supported by contemporary research. Precipitating factors include surgical intervention, acute infection, emotional trauma, local trauma, and certain drugs, such as penicillin, ergotamine tartrate, vitamin B_{12}, mercurial diuretics, and thiamine hydrochloride, each when administered intravenously. The prognosis in gout is excellent if the prophylactic regimen is followed. This involves the administration of colchicine and a uricosuric agent (probenecid) daily in moderately or severely afflicted patients and less often in those mildly afflicted. If the prophylactic regimen is followed, little or no incapacity needs result.

Deleterious Effect of Intra-articular Hydrocortisone. G. N. Chandler and V. Wright. Lancet 2:661-663 (Sept. 27) 1958 [London].

In a controlled trial of intra-articular steroid therapy in rheumatoid arthritis, both hydrocortisone acetate and hydrocortisone tertiary-butyl acetate were found to give significant clinical improvement lasting several weeks. Four injections of each drug and 4 of placebo were given into the knees over a period of 48 weeks, during which physical grading and functional capacity were measured every 2 weeks. Roentgenograms of the knees were obtained before and after the trial. Both drugs were more effective than the placebo, but despite the generally good clinical response to injections of the hydrocortisone preparations roentgenologic evidence of deterioration, sometimes considerable, was found in the knees of more than half of the patients so treated. Eighteen patients with 25 involved knees completed the trial. Roentgenologic deterioration was observed in 13 joints. Thus, intrasynovial injections of hydrocortisone and related compounds either failed to halt or, more usually, accelerated pathological changes, despite the clinical relief enjoyed by the majority of patients.

This apparent paradox of worsening disease in the face of clinical improvement was subjected to further investigation. No significant association could be traced between the effects of treatment on pain and the range of movement in the 2 groups of patients with and without roentgenologic progression of arthritis. An important difference between the groups was apparent, however, in respect to walking time; a trend toward greater improvement at the 2nd week after treatment in the group with deterioration became very significant at the 6th week. It must be concluded that the principal effect of treatment in this group has been the attainment of a standard performance beyond the capacity of the joint. The discrepancy between the effects on pain and walking time in the 2 groups was probably more apparent than real, for the quantification of pain is notoriously imprecise. The fact that it was not until the 6th week after treatment that improvement in walking time became significant in the group with roentgenologic deterioration suggests that the chief cause for roentgenologic progression was the encouragement of a damaging level of performance by interference with a normal, locally protective mechanism.

A Contribution to the Mycology of the Mouth. E. C. Fox and G. C. Ainsworth. Brit. M. J. 2:826-828 (Oct. 4) 1958 [London].

During recent years particular attention has been paid to mycotic infections of the oral cavity as a complication of antibiotic therapy. In an effort to supply data on the mycology of the mouth in relation to a number of fairly common oral lesions, isolations of fungi were made from patients at Birmingham Dental Hospital during 1952 to 1955 to ascertain whether there were any relationships between fungi and these oral disorders. The isolations were made in the clinic by inoculating slopes of malt extract agar with scrapings taken with a sterile scalpel. Incubation was at 20 to 25 C, and any fungi which developed were obtained in pure culture for identification. Bacteria and actinomycetes were ignored. Twenty-six of 175 patients were

excluded from further study, because they had conditions which showed no distinctive mycological findings, such as lichen planus, lupus erythematosus disseminatus, leukoplakia, fungating antrum carcinoma, and dry socket. The remaining 149 patients were grouped as having 6 clinical conditions, namely, angular cheilosis, gingivostomatitis (comprising aphthous, herpetic, acute ulcerative, mycotic, and various stages of inflammatory periodontal conditions), lingua nigra, lingua geographica, coated tongue, and denture sore mouth.

In some persons of the control series (groups of school children, university students, and professional and office workers) isolations were made as in the patients, but in others saliva was sampled by a single swabbing of the tongue, gums, and teeth and by streaking plates or slopes of malt agar with the swab. From the mycological findings in the 149 patients with angular cheilosis, gingivostomatitis, lingua nigra, lingua geographica, coated tongue, and denture sore mouth, it is concluded that Candida albicans seems to play a primary part in the etiology of angular cheilosis and has some connection with the etiology of gingivostomatitis. The diverse fungi associated with the remaining 4 conditions are of uncertain etiological significance.

Rheumatoid Arthritis of the Cervical Spine in the Adult. J. Sharp, D. W. Purser and J. S. Lawrence. Ann. Rheumat. Dis. 17:303-313 (Sept.) 1958 [London].

The authors studied the roentgenologic changes produced in the cervical spine by rheumatoid arthritis in adults, and they also investigated whether such changes may occur as the only evidence of rheumatoid arthritis, that is, without clinical or roentgenologic signs of the disease elsewhere. A series of lateral roentgenograms of the cervical spine from 44 hospital patients, aged 55 to 64 years, who had rheumatoid arthritis were compared with a series from persons of the same age and sex distribution selected at random from the general population. The films from rheumatoid subjects showed more narrowing of the upper cervical disks. This disk narrowing was more often associated with erosion of the vertebral plates and less often with sclerosis or osteophyte formation, and in the apophyseal joints there were more destructive changes. The roentgenograms from nonrheumatoid subjects showed more proliferative changes. In rheumatoid subjects, vertebral subluxations were more frequent and more severe at all levels of the cervical spine.

With the use of these criteria, a series of 428 cervical roentgenograms from random samples of the population were graded for the changes of cervical rheumatoid arthritis. Definite evidence of rheumatoid arthritis was found in the roentgenograms of 6% of the men and 7% of the women. There was a relationship between the roentgenologic grading for rheumatoid arthritis in the cervical spine and a positive sheep-cell agglutination test. There was little or no correlation between these roentgenologic gradings for cervical rheumatoid arthritis and either morning stiffness or a clinical diagnosis of rheumatoid arthritis, or with a diagnosis of rheumatoid arthritis made in accordance with the criteria of the American Rheumatism Association. There was, however, an association between roentgenologic signs of rheumatoid arthritis in the cervical spine and similar signs in the hands and feet. A cervical form of rheumatoid arthritis without peripheral joint involvement may account for an important number of apparently false-positive reactions in the sheep-cell agglutination test.

Clinical-Neurological Study of 21 Cases of Botulism. C. Castedo, M. Hermida and H. Puricelli. Acta neuropsiquiát. argent. 4:118-126 (April-June) 1958 (In Spanish) [Buenos Aires].

An outbreak of botulism in 21 patients who ate canned pimentos in the same restaurant in La Plata, Argentina, between June 2 and 6, 1957, is reported. Toxicity of the suspected food was proved by feeding it to animals. There were 12 fatal and 9 mild cases. The period between ingestion of the toxic food and appearance of symptoms varied between 14 and 48 hours. The early symptoms consisted of nausea, vomiting, dizziness, headache, and asthenia. In patients with severe intoxication, the early symptoms were followed by blurred vision, mydriasis, ptosis, diplopia, strabismus, lack of or delayed pupillary responses, and paralysis of several cranial nerves. In patients with mild intoxication, the predominant symptoms were exclusively oculomotor.

The treatment of these patients consisted of the administration of antibotulinic serum which was specific for types A and B of Clostridium botulinum. The serum was titrated in 2,000 units per cubic centimeter and was administered according to the following scheme: All patients had an intramuscular injection of 10 cc. (20,000 units) of the serum as soon as they reported to the hospital. If ingestion of the toxic food had been moderate and the symptoms abated during a week, a second and final intramuscular injection of the same dose of antibotulinic serum was given, and the patient was discharged. If ingestion of the food had been considerable but the symptoms had diminished after the first injection of antibotulinic serum, the injections were repeated at certain intervals; they were given intramuscularly up to a total dose which varied between 60,000 and 200,000 units. Patients who were hospitalized in a grave condition were given a total dose of 320,000 units of the anti-

botulinic serum, which was administered as follows: 100,000 units intramuscularly, 200,000 units intravenously, and 20,000 units intrathecally.

Antibotulinic serum therapy was given with the necessary precautions of testing the tolerance of the patients and in association with antihistaminic drugs. Ten of the 12 severely ill patients were treated also with ganglionoplegics and barbiturates as a preliminary to placing them in the pulmotor. Specific antibotulinic serum therapy failed to save the 12 patients who were hospitalized with acute symptoms of severe intoxication. This group included a patient in whom the treatment was started before the appearance of oculomotor symptoms. The botulism toxin seems to block the nonmyelinated endings of the nerve fibrils at the motor plate, inhibiting the production of acetylcholine which controls the neuromuscular synapsis.

SURGERY

Osteogenic Sarcoma of the Jaws and Facial Bones. L. V. Kragh, D. C. Dahlin and J. B. Erich. Am. J. Surg. **96**:496-505 (Oct.) 1958 [New York].

The authors report on 9 male and 10 female patients, between the ages of 11 and 60 years, with osteogenic sarcoma of the mandible, on 10 men and 4 women, between the ages of 16 and 62 years, with osteogenic sarcoma of the maxilla, and on 6 men and 5 women, between the ages of 15 and 55 years, with osteogenic carcinoma of the antrum and ethmoid region, who were treated at the Mayo Clinic before March, 1957. Most of the patients were treated surgically with or without adjunctive irradiation therapy. Several patients who received limited surgical treatment elsewhere were cured subsequently by more radical therapy, which consisted of wide surgical resection or diathermy destruction of the lesion and surrounding tissues. Eleven of the 44 patients were still living at the time of follow-up in March, 1957, and in addition 1 patient was known to be alive and well 6 years after treatment. Of the 35 patients treated before March, 1952, 11 are known to have lived for periods ranging from 5 to 28 years after their first definitive treatment at the Mayo Clinic. Six of these had mandibular, 4 had maxillary, and 1 had antral sarcoma. Of these 11 survivors, 5 had chondroblastic, 4 fibroblastic, and 2 osteoblastic osteogenic sarcomas. Neither patient with primarily ethmoidal involvement survived 5 years. Two patients died of recurrent tumor or metastasis 13 and 6 years, respectively, after their first treatment at the Mayo Clinic.

These data show that surgical treatment affords a reasonable chance of cure. A tendency to late systemic spread and a relatively low average degree of malignancy are among the factors that contribute to successful therapy. In the 44 patients symptoms were commonly present and led to many dental and minor surgical procedures before the correct diagnosis was established. This fact emphasizes that a relatively painless nonulcerating mass occurring in the upper or the lower jaw, particularly about an alveolus, should suggest the possibility of osteogenic sarcoma. In the antral and ethmoid regions, early symptoms are lacking. Roentgenographic examination is extremely helpful in most instances, but definitive diagnosis depends on histological studies. In 4 patients the sarcomas arose in regions previously irradiated for benign conditions of bone or soft tissue. More alertness on the part of dentists and physicians would favor earlier correct diagnosis and treatment of osteogenic sarcoma of the jaw.

Considerations and Comparisons of Ligation of the Internal Mammary Arteries: Operation According to the Technique of Davide Fieschi: Experimental Study. C. Zagnoni and P. Ziliotto. Acta chir. italica **14**:511-538 (July-Aug.) 1958 (In Italian) [Padua, Italy].

The authors investigated in dogs and in human beings the efficacy of the operation devised by Davide Fieschi for the treatment of coronary insufficiency. This operation consisted of ligation of the internal mammary arteries at the level of the second or the third intercostal space. After ligation a solution of turpentine oil and of ultrafiltered lead tetroxide (minium) was injected into the internal mammary arteries close to their origin, into the coronary arteries, or into the arteries of the pericardium to observe possible passage of the radiopaque substance to the vascular net of the pericardium. At the point of ligation of the internal mammary arteries only a slight and transitory increased blood pressure was observed. However, at the point of ligation a marked increase in the oscillometric rate was noted. It was accompanied by an increased flow into the main collaterals of the ligated artery, which included the pericardium-phrenic vessels. The pericardium-phrenic vessels did not, however, make any significant anastomotic connection with the coronary system. This was observed both in dogs and in human beings. It seemed that the increased flow in the pericardium-phrenic system was a normal and proportional compensation for the interrupted circulation of the main branch. This additional flow into the pericardial system was small and of practically no clinical advantage.

The ultrafiltered minium which was injected into the internal mammary arteries brought into relief the system of the arteries of the pericardium, and it penetrated into the coronary system only through a considerable circumvention. The additional pressure on the coronary system of both humans and dogs with a normal or a defective

heart was weak. Likewise, the ultrafiltered minium injected directly into the coronary system of both humans and dogs with a normal or a defective heart spread through many ascending branches of the coronary arteries but did not penetrate into the pericardial system. Consequently, this experiment demonstrated a relative independence of the arterial system of the pericardium from that of the coronary arteries. The authors suggest that for the treatment of coronary insufficiency it is better to apply surgical operations designed to establish a direct vascular connection between the arteries of the pericardium and those of the heart than to resort to ligation of the internal mammary arteries.

Clinical Comparison of Homografts and Braided Nylon in Arterial Bypass Surgery. R. P. Hohf, O. H. Trippel and H. Laufman. A. M. A. Arch. Surg. 77:552-560 (Oct.) 1958 [Chicago].

A group of 33 femoral and iliofemoral homografts were compared with a group of 23 Edwards-Tapp nylon prostheses in a series of 45 patients with bypass procedures. Of 33 homografts inserted, 13 remained patent, and 20 were failures; of the 20 failures, 9 occurred early and 11 late. The 23 nylon prostheses procedures resulted in 10 successes and 13 failures, of which 6 were early and 7 late. Poor distal run-off was considered the cause of 60% of the homograft failures and 54% of the nylon failures. A nylon prosthesis lasted 5 months in an exposed wound, but an exposed homograft softened and ruptured after only 2 weeks. Comparison of the results with homografts and with nylon prostheses in this small series of patients reveals no significant difference in the percentage of successful grafts in the 2 groups. Of the homografts, 39.4% were successful, and of the nylon prostheses, 43.5% were successful. However, a definite difference between the two is that the late failures in the homograft group were occasionally associated with defects developing in the graft itself, whereas late failures in the nylon group were never the result of inherent defects in the prosthesis. There were 5 complications caused by defects peculiar to homografts (3 ruptures and 2 aneurysms), but there were no such defects with nylon tubes.

Homografts, in general, are less durable than plastic tubes. Nylon, as used in this study, has shown no tendency toward weakness for periods up to 2 years. It seems likely that it will outlast the patient in most cases. The ideal prosthesis has not been developed as yet, but the nylon tubes used in this study have eliminated an important cause of graft failures from defects in the structure of the graft itself. Results of bypass surgery are also improved by careful selection of patients, with insertion of grafts only in the most suitable of them.

The Clinical Use of an Elastic Dacron Prosthesis. D. E. Szilagyi, L. C. France, R. F. Smith and J. G. Whitcomb. A. M. A. Arch. Surg. 77:538-551 (Oct.) 1958 [Chicago].

An arterial substitute woven of plain Dacron yarn in the woof and elasticized (Helanca) Dacron yarn in the warp in the form of straight tubes and bifurcations was used in animal experiments and in 43 clinical cases. The prosthesis is elastic, seamless, smooth-walled, finely porous, light, and soft and has the ability to elongate 15 to 20% without deformity. It is easy to procure, store, and sterilize. This prosthesis comes reasonably close to what is required, having a porosity that is satisfactory both from the point of view of arteriogenesis and from that of hemostasis. In animal experiments with long aortic bypass implants, during 11 months of observation the elastic Dacron prostheses showed an excellent rate of patency, even when traversing a tortuous course. Arteriogenesis around the implants was good, and tissue reactivity was low. During 9 months of implantation the initial tensile strength of the prostheses was essentially unchanged.

In considering the results of 9 months' experience with 43 cases, the prejudicial effect of case selection must be kept in mind, as patients with more advanced and diffuse disease were assigned for treatment with angioplastic procedures utilizing the prosthesis rather than for treatment by homograft. In spite of this, the Dacron prosthesis yielded a patency rate only slightly below that obtained with homografts. In angiographic examinations up to 9 months after operation, there was patency of the arterial substitute in 92% of the aortoiliac area grafts and in 63% of the femoropopliteal area grafts. In experiments on dogs there was some evidence that the new-formed lining of the prosthesis was slow to develop. Since the formation of this pseudointima was greatly influenced by the technique of preclotting (which is largely a matter of personal skill), the evidence in this regard was not entirely convincing. Moreover, in older canine specimens the new intima was always found to be satisfactory.

Another factor to be considered in examining results is the initial lack of full familiarity with the technical behavior of a new device. This study shows that results are better when angiographic visualization of the prosthesis is delayed until the 6th postoperative week.

The advantage of plastic prostheses consists in the promise that their rate of deterioration after longer follow-up periods will be much less than that of homografts. If this is true, the late patency rate of plastic implants will be better than that of homografts, since many more of the early good results will persist. The assumption that this is what will happen is supported by excellent experi-

mental evidence but will not be proved until the prostheses have been observed for much longer periods of time.

Scalene Node Biopsy—Clinical Evaluation and Application. S. W. Shapiro and L. T. Palumbo. Am. J. Surg. 96:511-514 (Oct.) 1958 [New York].

The authors performed scalene node biopsies on 51 patients with pulmonary lesions in the department of surgery of the Veterans Administration Hospital in Des Moines, Iowa, in the course of a 30-month period. Metastatic carcinoma in the scalene nodes was found in 9 (18%) of the 51 patients. Thirty-eight of the 51 patients had proved primary carcinoma of the lung, and biopsy of the scalene nodes revealed metastatic carcinoma in 7 patients (19%); 3 of the 7 patients had scalene nodes involved on the right side, and 4 on the left side. Scalene nodes were clinically palpable in 6 of the 38 patients with primary carcinoma of the lung. In 2 patients with palpable nodes, carcinoma was not found on microscopic studies. Of the 4 patients with positive biopsies of the scalene nodes on the left side, 3 had palpable nodes. Lesions of the upper lobe of the left lung accounted for 2 of these, and the third lesion was a left hilar mass. Of the 3 patients from whom positive scalene node biopsies were obtained on the right side, 1 had clinically palpable nodes, and the primary lesion presented as a right hilar mass. There were 3 patients in whom nodes were not palpable clinically, but metastatic carcinoma was found in the scalene node specimens. In the instances of nonpalpable scalene nodes, the incidence of positive nodes thus was 8.1%.

Of the 38 patients with proved primary carcinoma of the lung, 19 were considered to have operable disease and 19 were considered to have inoperable disease; from 2 (10%) of the 19 patients with operable disease, positive scalene node biopsies were obtained. This factor may be an important consideration in selection of patients for exploration and resectability. Scalene node biopsy is an additional adjunct to the establishment of a diagnosis in many lesions and an important aid in the determination and selection of patients with pulmonary lesions for thoracotomy. A properly performed scalene node biopsy should become a definite part of the over-all examination and evaluation of patients with pulmonary lesions, particularly those with primary carcinoma.

Pulmonary Tuberculosis and Gastric Resection. H. Neubert. Tuberkulosearzt 12:444-447 (July) 1958 (In German) [Stuttgart, Germany].

Interrelations between pulmonary tuberculosis and gastric resection were investigated in an extensive literature survey and in studies carried out by the author. Among 4,348 patients who had undergone gastric resection, 120 (2.7%) with pulmonary tuberculosis were found; and among 23,061 patients with pulmonary tuberculosis, 460 (2%) who had undergone gastric resection were found. During the years from 1955 to 1957 at the sanatorium with which the author is connected, 31 patients who had undergone gastric resection were found among 832 male patients with pulmonary tuberculosis (3.5%). In 25 of these patients the tuberculosis became manifest after the operation, while in 6 patients reactivation of the tuberculous process occurred within 4 weeks to 5 years after gastrectomy. Fourteen of the 31 patients required hospital treatment. Pulmonary resection had to be resorted to in 5 patients. In view of the fact that in 4 of these 5 patients serious postoperative complications developed, the author believes that pulmonary resection should be performed in gastrectomized patients only when absolutely necessary. It is suggested that nutritional and vitamin deficiencies, due to defective intestinal absorption after gastrectomy, impair the defense mechanism of the body and thus create favorable conditions for the development of tuberculosis of the lungs.

Ovariectomy and Adrenalectomy for Treatment of Metastatic Cancer of the Breast. J. B. Davis. Am. J. Surg. 96:492-495 (Oct.) 1958 [New York].

Of 389 women with metastatic cancer of the breast, whose cases were collected from the literature and who had undergone bilateral ovariectomy and adrenalectomy for palliation, 189 (48.7%) obtained a remission with reduction of pain, healing of ulcerated lesions as well as of pathological fractures, reduction in size of tumor masses and pleural and peritoneal effusions, and prolongation of useful life expectancy. Three patients died, an operative mortality rate of 7.9%. The author performed bilateral ovariectomy and adrenalectomy on 11 women, between the ages of 39 and 56 years, with metastatic cancer of the breast. There was a dramatic remission in 9 patients (82%), with no operative death.

Estrogens have been proved to be carcinogenic and have a decided role in the production and maintenance of many cancers of the breast. It can be seen that removal of the ovaries will rid the body of the primary source of estrogen and removal of the adrenals removes all the remaining supply. Bilateral ovariectomy and adrenalectomy are worthwhile operations in the palliative therapy of disseminated cancer of the breast in that they have a low operative mortality rate and prolong the useful life expectancy of nearly 50% of the patients. At present there is no clear-cut criterion useful in selecting patients for adrenalectomy. It seems apparent that any person afflicted with disseminated cancer of the breast should be considered a candidate for this form of therapy.

Hypophysectomy with Yttrium^{90} Implant. C. A. Gleadhill. Irish J. M. Sc. 6:432-433 (Sept.) 1958 [Dublin].

According to Gleadhill, it is difficult to obtain total pituitary removal by either hypophysectomy or implantation of radioactive material, and so he decided to combine the 2 procedures. The radioactive substance used is 8 to 12 mc. of radio yttrium (Y^{90}) in the form of a fine powder. It is a pure beta-emitter and has a half-life of 68 hours and a penetration of about 1 cm. through tissues. When mixing the Y^{90} powder in the operating room with a self-setting acrylic resin proved unsatisfactory, the author tried mixing the powder with bone wax and later with dental impression wax, and this last method has proved consistently satisfactory. The operation is done through the standard frontal pituitary approach. A small skin flap is turned from just above the glabella to just in front of the ear, the bone is burred and sawn, the lower saw-cut being as close to the floor of the anterior fossa as possible, and the bone is left hinged on the temporal muscle. A thick piece of temporal muscle is removed and put aside for later use. When both nerves and chiasma are well displayed, the pituitary stalk is divided. The points of a long-angled forceps are pushed through the aperture in the diaphragma sellae and opened. With the aid of small curettes and pituitary rongeurs, the pituitary gland is removed piecemeal. When removal is believed complete, the plunger is used to force the wax into the apparently empty fossa. A flat spatula is now used to press it in, so that it is fully in contact with the walls of the fossa, and to smooth the upper surface. The piece of temporal muscle previously removed is now laid over the wax, between it and the optic nerves and chiasma, and Gelfoam is laid over the muscle. Since muscle has been used, no visual complications have occurred.

Transverse Incision in Abdominal Surgery of the Colon and Rectum. H. D. Trimpi. Dis. Colon & Rectum 1:339-344 (Sept.-Oct.) 1958 [Philadelphia].

This report concerns 250 consecutive cases of lesions of the colon and rectum in which transverse abdominal incision was employed. There were 151 patients on whom resections for carcinoma were performed. Resections for diverticulitis numbered 43. There were 32 colostomies accompanied by colonoscopic examination for polyps. The remaining 24 operations were performed for Hirschsprung's disease, villous adenomatous polyps, strictures associated with lymphogranuloma venereum and radiation proctitis, and for the purpose of determining whether there was recurrence of malignancy by "second look" operations. Advantages of the transverse abdominal incision, when employed in surgical procedures for lesions of the rectum and colon, are excellent exposure, diminished depth of the wound and easy access to the entire pelvis, less postoperative discomfort, a stronger wound and lower incidence of dehiscence, evisceration, and incisional herniation. Retention sutures, tight taping, and abdominal binders are not required. Early ambulation and deep breathing are facilitated. There is a shorter period of convalescence, and rehabilitation is possible earlier. The final result is a strong narrow scar, which is least displeasing cosmetically.

Carcinoma of the Breast in Middletown, U. S. A. T. C. Moore, D. R. Judd and W. C. Moore. Surg. Gynec. & Obst. 107:433-441 (Oct.) 1958 [Chicago].

The authors report their experience with 307 consecutive cases of histologically verified carcinoma of the female breast studied during a 16-year period, 1935-1951, at the Ball Memorial Hospital in Muncie, Ind. None of the patients were lost to follow-up, and all living patients have been followed for a minimum of 6 years. The Ball Hospital, during the period of this study, was a general hospital of 250 beds and was the only hospital serving Muncie (the "Middletown" of sociological literature), with a population of 60,000, and Delaware County, with a population of 95,000. It provided care for both private and charity patients. Carcinoma of the breast accounted for approximately 10% of the cases of malignant neoplasm handled at this hospital. Although the ages of the patients ranged from 22 to 90 years, 71% were between 40 and 70 years of age. All but 2 of the 307 patients were seen initially at the hospital. Carcinoma was found in the left breast in 160 of the primary cases and in the right breast in 140. Bilateral mammary involvement was encountered in 5 patients.

The Halsted type of radical mastectomy was carried out in 271 of the 305 primary cases (89%). Simple mastectomy was performed in 31 cases, and biopsy only was undertaken in 3. Simple mastectomy was reserved largely for the more elderly patients. The 2 with secondary disease received treatment for local recurrences. All the patients were operated on by specialists in surgery. One hundred ninety-seven of the patients are known to be dead, and 110 are living. Additional primary carcinomas were discovered in 5 of the patients. The 5-year survival of the total group of 307 patients was 54%. The 5-year survival of the 271 patients managed by radical mastectomy was 55%, while that of the smaller simple mastectomy group was 45%. The presence or absence of axillary nodal metastasis was found to be the most important single factor influencing the survival of the patient. Axillary metastasis was encountered in 52% of the patients managed by radical mastectomy. The 5-year survival in this group of patients was 73% without axillary metastasis and only 31% when axillary involvement could be demonstrated.

Radiation therapy, in amounts ranging from 1,800 to 2,000 r, was given after radical mastectomy to 57 patients. There was no apparent improvement in the 5-year survival of the patients who were found to have no axillary metastasis. However, in the group of 104 patients with axillary metastasis who were managed without postoperative radiation therapy, the 5-year survival was 34% as compared with a 53% survival in the relatively small group of 36 patients with axillary involvement who received postoperative radiation therapy. Greater utilization of postoperative radiation therapy in the currently employed 5,500 to 6,000 r range, especially in patients with axillary nodal metastasis, would appear to be worthy of more extensive trial. Ten-year follow-up was obtained in 100% of 184 consecutive patients. Thirty-three per cent of this group were alive 10 years after operation. Radical mastectomy was carried out in 164 of these patients, with a 44% 10-year survival in patients without axillary metastasis and a 22% survival in patients with axillary nodal involvement. The value of 10-year follow-up studies in assessing the results of management of carcinoma of the breast is emphasized.

Adrenalectomy in Cushing's Syndrome: Management and Metabolic Aspects. A. S. Mason, J. E. Richardson and C. E. King. Lancet 2:649-656 (Sept. 27) 1958 [London].

Adrenalectomy should be undertaken only when the diagnosis of adrenal cortical hyperfunction (Cushing's syndrome) is proved beyond doubt. Difficulty may be encountered in adolescent girls who exhibit obesity, acne, pink striae distensae, menstrual irregularity, and even a slight rise in blood pressure. There may be some increase in the urinary metabolites of hydrocortisone, but the absence of muscle wasting and the presence of generalized obesity help to distinguish this condition from Cushing's syndrome. These patients should not be subjected to adrenalectomy, as the disturbance is transitory and responds to a reducing diet. A similar type of benign transient disturbance is sometimes seen in young men. The adrenogenital syndrome in women is more serious. It arises in puberty and continues throughout life. Such patients are plethoric, hirsute, obese yet muscular, with irregular menstruation and, in later years, benign hypertension. Urinary steroid excretion is increased, but this is mainly in the form of 17-ketosteroids. However disfiguring, the disease is not fatal, and therefore adrenalectomy is seldom justified.

Cushing's syndrome, however, is a progressive fatal disease. Studies are reported on 17 patients in whom Cushing's syndrome was associated with adrenal hyperplasia and on 1 patient in whom it was associated with adrenal carcinoma. Special metabolic studies, including nitrogen and potassium balances, were made before operation in 8 patients and after adrenalectomy in 9. Patients were selected for adrenalectomy only when the diagnosis of Cushing's syndrome was beyond doubt and the disease was definitely progressive. Assessment of rate of progress was based on clinical features, such as hypertension, muscle wasting, and weakness, together with the data obtained from metabolic studies of protein catabolism and electrolyte disturbances. There are at present no adequate methods of restoring protein levels. The electrolyte disturbances must be corrected before operation.

Total adrenalectomy is recommended in younger patients and in those with rapidly progressive disease. In older patients subtotal adrenalectomy is preferred. In younger patients the operation is carried out in 1 stage and in older patients in 2 stages. The most important item in the immediate preparation for surgery is administration of sufficient cortisone to maintain the excessive level of glucocorticoids to which the patient has become accustomed. To ensure absorption over the time of operation and during the postoperative period, the cortisone must be given intramuscularly. Intake of water and sodium must be limited in the immediate postoperative period. The dose of cortisone must be gradually reduced, and later the amount of salt increased. The most serious postoperative complication is acute adrenal failure. It should be treated by giving hydrocortisone hemisuccinate, which should always be available in case of emergency. The other complications are ileus, pulmonary embolism, hemothorax, and pneumothorax.

Lobectomy for Postpneumonic Lung Abscess in Infancy and Childhood. T. C. Moore. Surgery 44:741-751 (Oct.) 1958 [St. Louis].

The author reports on 2 infants, a 7-week-old boy and a 16-month-old girl, and on a 9-year-old girl who were subjected to 4 lobectomies for lung abscess. In the 7-week-old infant emergency lobectomy was necessary because of tension pneumothorax due to communication of the abscess with both the tracheobronchial tree and the pleural space. A second, noncommunicating lung abscess occurred in this infant one month after the first operation and was also successfully managed by lobectomy. In all 3 patients the abscess was postpneumonic, and in all it appeared to be caused by Staphylococcus pyogenes var. aureus. The causative agent was cultured from the respiratory tract in all 3 patients and from the contents of 3 of the 4 abscess cavities. No growth could be obtained from the contents of one cavity after 5 weeks of intensive antibiotic therapy. All the abscess cavities were quite large, and all were lined with granulation and fibrous tissue. A communication with the tracheobronchial tree was observed only

in the infant boy. The initial symptoms in all 3 patients were of respiratory tract infection with fever of 2 to 4 weeks' duration before admission to hospital. In none of the patients was there any discharge of purulent material from the tracheobronchial tree before the operation. The lung abscess occurred during the Asian influenza epidemic of late 1957 and early 1958 in the 2 female patients; in both, bilateral pneumonitis had been shown by the chest roentgenograms before the formation of the abscess. The cases of these 2 patients were characterized initially by remissions and exacerbations of respiratory tract infection and attacks of marked hyperpyrexia. Lung abscess, particularly of the postpneumonic type, rarely occurs in infancy and childhood. The 2 infants in whom pulmonary resection for lung abscess was required were the only ones on an active pediatric surgical service during an 11-year period (1947-1958) at the Indiana University Medical Center in Indianapolis.

Digital and Instrumental Commissurotomy in Mitral Stenosis: A Study of 2,000 Cases. A. M. Dogliotti, A. Actis-Dato and R. Gentilli. Surgery **44**:706-717 (Oct.) 1958 [St. Louis].

The authors report on 2,000 patients who underwent mitral commissurotomy at the clinic for cardiac surgery of the University in Turin, Italy, between 1951 and 1957. Of the 2,000 patients, 987 were operated on by digital splitting only of the commissures; in 556 patients both commissures yielded, in 413 only the anterior yielded, and in 18 only the posterior did. Instrumental commissurotomy only was performed on 396 patients; in 112 patients both commissures were incised; in 248 only the anterior, and in 36 only the posterior. A combined technique was used in the remaining 617 patients; in 395 of them finger fracture and instrumental valvulotomy was applied to both commissures, while in the other 222 one commissure was split by digital fracture only and the other by instrumental valvulotomy only. In general, the anterior commissure was the most frequently divided, whether by finger fracture or by instrumental incision.

In the first 1,000 patients operated on, the enlargement of the mitral orifice obtained by the intervention was smaller than in the next 1,000 patients operated on. With more knowledge of the pathological anatomy of the mitral valve and more experience with the techniques of commissurotomy, greater enlargement of the mitral orifice was obtained. The greater the enlargement, the better was the functional result. Therefore, the authors attempted to enlarge the mitral orifice to a surface size as near to normal as possible. Minimal or moderate mitral insufficiency was recognized at the time of digital exploration of the mitral valve in 276 patients; it remained unchanged postoperatively in most of them; it diminished or disappeared in 29, and it increased in 53. In 36 patients an insufficiency of variable degree was created. Lacerations including the whole atrial wall occurred in 3 patients, and lacerations limited to the point of insertion of the left auricular appendage into the left auricle occurred in 54. All the lacerations, except 2, occurred during digital splitting maneuvers. There were 61 operative deaths (3.05%); of the 61 deaths, 20 (4%) occurred among the first 500 patients, 19 (3.8%) among the second 500, 15 (3%) among the third 500, and 7 (1.4%) among the fourth 500 patients operated on. Of 1,210 patients with elastic valves, death occurred in 30 (2.48%). Of 335 patients with calcified valves, death occurred in 19 (5.67%). Of 455 patients with sclerotic valves, death occurred in 12 (2.87%). Thus, the over-all mortality was lowest in the group of patients with elastic valves and highest in those with calcified valves.

The results obtained with instrumental commissurotomy, either as the sole technique or associated with digital pressure, were definitely better than those obtained with the single finger fracture technique because of the better functional mobility obtained and also because of the lower incidence of complications. There were no particular differences in the mortality rate according to the techniques employed; the mortality seemed to be more related to the anatomic condition of the stenotic valve. Instrumental valvulotomy is not always necessary, but it is suggested in the presence of sclerotic commissures resistant to digital pressure and extensive calcifications of the commissures. It is a safe procedure. For restoration of maximal cusp mobility one should attempt to extend the incision of the commissure up to the optimal limit which is represented by the fibrous ring. The Dogliotti valvulotome proved to be the simplest instrument and the easiest to handle.

Use of Nylon Bifurcation Grafts in Arteriosclerosis. L. D. Hill, G. H. Lawrence and L. Annest. West. J. Surg. **66**:276-281 (Sept.-Oct.) 1958 [Portland].

One of the most effective methods of treating aneurysms or obliterative arteritis of arteriosclerotic origin affecting the abdominal aorta and its bifurcation is either the resection of the diseased segment and its replacement by a bifurcation graft or a complete bypass of the obstruction by a graft. Attempts have been made to overcome the difficulty of obtaining and preparing satisfactory homologous arterial grafts by the use of various synthetic materials. One of the most recent and, in the authors' experience, most satisfactory types of grafts has been the Edwards-Tapp nylon graft. This is a braided nylon, Silicone-treated, bifurcation graft which is seamless and has crimped tub-

ing to prevent wrinkling in the iliac branches. The seamless construction does away with the possibility both of leakage through a broken-down seam and of thrombosis in the seams in the smaller branches. Branches of crimped tubing can be bent to form a side-to-end anastomosis without kinking, and in grafts below the inguinal ligament, the crimping prevents thrombosis from occurring when the hip is bent. One disadvantage of the nylon graft, on the other hand, is the fact that it is porous and begins to leak as soon as the clamps are released from the aorta. This disadvantage can be offset, however, and the blood loss can be minimized if the graft is preclotted before it is put in place. Another slight disadvantage is the fact that the ends of the nylon graft must be cauterized in order to keep them from fraying when they are sewed in place. Even after being cauterized, the graft tends to fray at the end unless it is handled very carefully.

Failure of the graft itself did not occur in any of the 20 patients in the authors' series, 12 of whom had occlusive disease and the other 8, aneurysms. One of the patients with occlusive disease died, 9 had excellent results, and in 2 claudication, though not eliminated, was considerably lessened. Two patients had ruptured aneurysms. One recovered and is now working at his previous job without symptoms, although he suffered a myocardial infarction during the postoperative period. The second patient underwent a successful resection and graft of the ruptured vessel, but thrombosis of the right posterior tibial artery appeared and made it necessary to perform an arteriotomy on the first postoperative day. This procedure was also successful, but on the 7th postoperative day the patient died of a pulmonary embolism. One other patient, who was operated on for an aneurysm, died 8 months after the original operation when a second intervention became necessary because of a leak in the proximal anastomosis. It is true this represented failure of a suture line, but it did not represent failure of the graft, because it appeared that the aorta had become necrotic proximal to the anastomosis. Follow-up of the surviving patients with aneurysms showed them to be in good health and without symptoms referable to the arterial tree.

The Effects of Hypophysectomy on Intellectual Functioning. M. Schon. J. Ment. Sc. **103**:743-748 (July) 1958 [London].

When hypophysectomy was first employed, it was speculated that patients undergoing this type of surgery might become intellectually so deteriorated that the benefit of the prolongation of the life span might be offset by the possible mental incapacity. In addition, most of the patients who were faced with this type of surgery raised the question as to the possibility of mental deterioration after hypophysectomy. These considerations gave impetus to the present study. Hypophysectomy involves 2 variables: brain surgery, and the elimination of the major source of endocrine stimulation and hormone production. On the basis of literature reports, it was hypothesized that hypophysectomy will not effect any significant changes in intellectual functioning, nor that it will result in brain damage.

Twenty women, ranging in age from 40 to 66 years, who had metastatic malignant breast tumors suspected to be dependent upon endocrine gland factors were studied before and after hypophysectomy. All the patients were tested with the Wechsler-Bellevue Intelligence Scale preoperatively and 6 to 10 weeks postoperatively. The Wechsler-Bellevue Intelligence Scale consists of a verbal scale and a performance scale. No statistically significant change in general intellectual functioning and no brain damage, as measured by the tests, could be noted after hypophysectomy. Thus, the hypothesis was confirmed. There was an increase in accuracy, possibly as a result of postoperative improvement in health or due to the practice effect involved in retesting, and a decrease of speed, probably related to a secondary hypothyroidism because of a deficiency of pituitary hormones.

Congenital Cystic Dilatation of the Common Bile Duct: Special Reference to Radiographic Studies. M. M. Ravitch and G. B. Snyder. Surgery **44**:752-765 (Oct.) 1958 [St. Louis].

The authors report 3 cases of choledochal cyst, or congenital cystic dilatation of the common bile duct, in a 3½-month-old female infant and in 2 girls, aged 5 and 13 years respectively. The infant had jaundice since the third week of life and a huge choledochal cyst, for which she was successfully treated by a Roux-Y anastomosis of cyst and jejunum. The 5-year-old girl, with attacks of pain, jaundice, and a palpable mass in the right upper quadrant of the abdomen, had a largely retroduodenal cyst, which was anastomosed to the duodenum with relief of symptoms. In the 13-year-old girl with repeated attacks of violent epigastric pain but without a palpable mass or jaundice, the choledochal cyst was shown preoperatively by an oral cholecystogram, and an intravenous cholangiogram made before the operation confirmed the findings of the cholecystogram. At surgical intervention the cyst was demonstrated clearly by 10 cc. of a 50% solution of diatrizoate (Hypaque) sodium injected into the gallbladder. Two additional injections of 10 cc. and 5 cc. of the contrast medium showed the hepatic and common ducts and also the pancreatic duct. The last injection of the contrast medium was discontinued when resistance was noted, and the gallbladder was seen to be

tense for the first time. A precipitous fall occurred in the patient's arterial pressure from 110 to 50 mm. Hg, but withdrawal of 20 cc. of thin bile-colored fluid from the cyst resulted in immediate restoration of normal arterial pressure. A cystoduodenostomy gave relief, but clinical pancreatitis resulted from the injection of the contrast medium in an attack simulating the preoperative attacks. The patient's subsequent course was smooth, and she has remained well for 5 postoperative months.

The diagnosis of choledochal cyst can usually be made on the clinical grounds of recurrent pain and jaundice and a palpable abdominal mass and can occasionally be confirmed by preoperative roentgenographic studies. The diagnosis may be made with absolute precision at surgical intervention by the injection of contrast medium into the gallbladder. The nature and cause of the anomaly remain uncertain. The facts that jaundice eventually supervenes, even though characteristically intermittent, and that dilatation of the hepatic ducts was observed in all 3 patients and was described in other cases collected from the literature indicate an obstructive element. The acute pancreatitis, which was inadvertently produced in the third patient by retrograde injection of the contrast medium under pressure, precisely duplicating her preoperative attacks of pain, made it obvious that injections of contrast medium into the cyst in these patients should be done under gravity with little or no pressure. The small, or largely retroduodenal, cyst should be treated by direct anastomosis between the duodenum and the cyst, and the larger cyst by a Roux-Y anastomosis to the jejunum.

Carcinomatous Degeneration of Pilonidal Cysts: Report of a Case. J. G. Matt. Dis. Colon & Rectum 1:353-355 (Sept.-Oct.) 1958 [Philadelphia].

In an 18-year-old youth who complained of pain and bleeding from the rectum, several pinpoint openings were discovered over the sacrococcygeal junction. A diagnosis of pilonidal cyst with perirectal fistula was made, and the cyst and its ramifications were excised and the wound marsupialized. The pathologist diagnosed a mixed basal-cell and squamous-cell carcinoma of the perianal skin and of the pilonidal sinus tract. One month later, the entire scar and the granulating area were excised en bloc, including a generous cuff of normal tissue on all sides and extending down to the periosteum and the gluteus maximus muscle and into the ischiorectal fat. Marsupialization of the wound was again performed. Microscopic examination of the specimen revealed no evidence of neoplasia.

The author considers it remarkable that a lesion as common as pilonidal cyst (which, moreover, may be the result of embryologic vagary or of cicatrix formation [both have been mentioned as precursors of malignancy]) should become involved by malignant degeneration so infrequently. It was suggested by Hall and Lee that failure to detect cancer more often in specimens of pilonidal disease may be owing to inadequate microscopic examination. The author believes that pilonidal disease, with chronic drainage or recurrent acute inflammation, requires a surgical procedure that will completely eradicate all involved tissue and that this tissue should be submitted to a histological examination.

The Surgical Patient: Oral Bouillon Feedings. H. B. Benjamin, M. Wagner, N. L. Bugarin and G. Bartenbach. J. Internat. Coll. Surgeons 30:405-411 (Oct.) 1958 [Chicago].

It is now common practice to use the vascular system for alimentation during the postoperative period. To maintain the surgical patient in the ideal state of protein and electrolyte balance requires a great deal of cooperative work among the surgeon, the nurses, and the laboratory staff. If any one of the persons concerned with this program fails to meet his or her obligation, or if a bottle of urine or material obtained by gastric suction is spilled, the entire venture fails. Add to this the great financial burden placed on the patient, and the result is a cumbersome program of scant value to the patient. The numerous phlebotomies and the intravenous administration of massive quantities of fluids was presented by Bailey as the cause of many so-called undiagnosed, or falsely diagnosed, deaths that have been ascribed to the surgical procedure but that are actually due to air emboli. The intravenous infusion of nutritional fluids does not guarantee that the body has accepted and utilized them. Far more stress is placed on keeping the patient in electrolyte and nitrogen balance by intravenous infusions after an operation than is necessary or advisable.

A simple approach would be to administer orally some liquid form of food that would be well tolerated and appetizing and would supply the electrolyte and protein needs of the patient. Beef bouillon broth was selected as being the substance most aptly filling these requirements. Several types of bouillon cubes were tested, and the one selected contained 26.2% of protein, 6.6% of fat, and 10.3% of other organic matter. Two cubes were dissolved in 300 cc. of hot water, and this was given to the patient every 3 hours, starting on the first postoperative day. This broth was well tolerated and induced and increased the appetites of patients; at the same time, the hot fluid encouraged intestinal peristalsis. A comparative study was made on patients, most of whom had undergone total or partial gastric resection. Their ages ranged from 30 to 75 years. Blood was drawn on the day the patient entered the hospital for chemical tests; this supplied preoperative blood levels for comparison. Bouillon broth was ordered on the first postopera-

tive day and successive days until the patient was ready for discharge from the hospital. By comparison with patients who received electrolyte therapy parenterally, the administration of bouillon by mouth provided and maintained the same, or better, electrolyte and protein blood levels as did the electrolyte parenteral program. It is not meant to imply that the bouillon feedings are the answer to all problems of postoperative nutrition, but in the opinion of these authors they have several advantages over intravenous feeding and can be a simple and inexpensive approach to a great many nutritional problems of postoperative care.

GYNECOLOGY & OBSTETRICS

Pregnancy After Pneumonectomy for Pulmonary Tuberculosis: Analysis of a Collected Series of Seventy-four Pregnancies in the Netherlands. C. D. Laros. Am. Rev. Tuberc. 78:563-569 (Oct.) 1958 [New York].

Young women who have undergone pneumonectomy often ask their physicians, "Is it sensible to marry, and is there any objection to having children?" To obtain some insight into this problem, a survey was made of the frequency and course of pregnancy in female patients after pneumonectomy for pulmonary tuberculosis. Inquiry produced data on 64 patients from all parts of The Netherlands who had a total of 74 pregnancies. Generally speaking, no adverse effects of the operation for either the mother or the child were seen during pregnancy and labor.

Topical Androgenic Hormones in Vulvar Kraurosis-Leukoplakia Syndrome: Preliminary Report. A. C. Richardson and G. A. Williams. Am. J. Obst. & Gynec. 76:791-799 (Oct.) 1958 [St. Louis].

The authors present a preliminary report on 25 women, their ages ranging from 25 to 89 years, with kraurosis and/or leukoplakia of the vulva, who have been treated primarily with topical testosterone propionate in sesame oil in a petrolatum base. Three patients were referred from charity clinics, and the remaining 22 were private patients. Twenty-four of the 25 patients were, or had been, married and, of these, 19 were parous. Nineteen of the patients had had previous treatment, but in none of them had the disease been satisfactorily controlled. Two patients had had previous vulvectomies, one for carcinoma of the vulva and the other for leukoplakia of the vulva. Both of these had postoperative recurrence of leukoplakia with pruritus. Fifteen of the 25 patients had primary atrophy (kraurosis), 4 had leukoplakia, and 6 had primary atrophy with leukoplakia. Patients who presented a severe inflammatory reaction of the vulva with intense pruritus were initially treated with 0.1% fluorocortisone acetate ointment as an anti-inflammatory agent. Its use was discontinued as soon as the inflammatory reaction improved. The patients were then instructed to apply to the vulva the testosterone propionate–oil preparation, 10 cc. of which (50 mg. of testosterone propionate per cubic centimeter) was combined with 10 Gm. of white petrolatum. Oral or parenteral therapy with estrogen was not prescribed. No lesions were excised except for biopsy; no surgery was done for contracture of the introitus. Four patients had incision of a vaginal phimotic foreskin under local anesthesia. All 25 patients were followed for a sufficient period, varying from 3 months to 6½ years, to judge the efficacy of the treatment. One of the 25 patients has been lost to recent follow-up, but the remaining 24 are still under observation.

All 25 patients received satisfactory symptomatic relief of their pruritus and irritation within 1 to 6 weeks, accompanied by healing of abrasions and fissures. Grossly leukoplakic plaques regressed, although some required several months. All patients had a return of symptoms and progression of the disease within 1 to 6 months after omission of the testosterone ointment. Continued therapy thus has been required. None of the patients showed evidence of hirsutism, voice changes, or acne, even after prolonged therapy. All had some hypertrophy of the clitoris, which persisted and prevented the recurrence of phimosis. Depigmented areas of the vulvar skin were not observed to have a return of pigment. There has been no allergy due to the medication. Several of the patients developed an intertriginous dermatitis of the vulva during the early weeks of therapy. This disappeared under symptomatic treatment and did not recur with continued use of the testosterone ointment. Satisfactory relief of symptoms, without recourse to surgery, and apparent arrest of the disease process have been accomplished with this method of treatment.

The Possible Role of Smegma in Carcinoma of the Cervix. H. C. Heins Jr., E. J. Dennis and H. R. Pratt-Thomas. Am. J. Obst. & Gynec. 76:726-735 (Oct.) 1958 [St. Louis].

The authors performed experiments on mice into whose cervices and upper vaginas raw human smegma, obtained by retraction of the foreskin and evacuation of this material from about the glans in uncircumcised male inmates at the South Carolina State Hospital in Columbia, was applied repeatedly by 2 basic methods; these methods were by means of a metal speculum and by the injection of a single "dose" into the vagina followed by closure of the vaginal orifice with sutures. Biweekly vaginal injections of culture of 100% Mycrobacterium smegmatis and biweekly injections of 100% Myco. smegmatis in culture with 5% cholesterol also were performed on mice. Of 88 mice used for

the injection of raw smegma followed by vaginal ligation, epidermoid carcinoma occurred in 8 (10%) and marked hyperplastic changes in 22 (25%). Thus, there were significant changes in 35% of the animals. These results show that carcinoma of the cervix can be produced by human smegma if the stimulus is continued for 14 months or more. Whole smegma, as well as some of its components, is stimulatory to the cervicovaginal epithelium of mice, and invasive carcinoma will eventuate if the stimulus exists. Whole raw smegma has proved to be the most effective stimulus in these experiments. The objections to the use of lower animals in reference to human cancer are obvious. A similar study with the use of an experimental animal of primate level is contemplated.

The Origin of Fetal Malformations: The Case of a Rare Monster. F. De Gennaro. Minerva ginec. **10**:543-551 (July 31) 1958 (In Italian) [Turin, Italy].

A woman, 38 years of age, was delivered of a stillborn monster at the 7th month of pregnancy, after previously having had 3 normal children. The history of the parents revealed nothing unusual, except that the mother was underfed during pregnancy. The newborn infant had normal extremities, mouth, and ears but a short neck and no nape. A large eyeball with 2 pupils was set in a cavity in the middle of the upper third of the face. A small fleshy protrusion, 2.5 cm. (1 in.) in size, rose just above the eye cavity. Behind the protrusion, a large, dark, vesicular mass replaced the skull and extended over the posterior part of the neck. The ribs showed defective development and absence or fusion of parts. The skull had the frontal bone, but the ethmoid, vomer, inferior nasal conchae, lacrimals, and nasal bones were absent. The encephalon was not divided into hemispheres but consisted of a single vesicle.

Surgical and Radiologic Treatment of Cancer of the Cervix in 397 Cases. H. C. Frick II, J. A. Corscaden, H. W. Jacox and H. C. Taylor Jr. Surg. Gynec. & Obst. **107**:457-468 (Oct.) 1958 [Chicago].

After 1944 radical surgery was reintroduced into the program for treatment of cancer of the cervix in the hope that its use in appropriate instances would increase the number of cures. This report is concerned with 397 patients who were admitted with a diagnosis of carcinoma of the cervix to 2 New York hospitals, the Sloane Hospital for Women, from 1944 to 1951 inclusive, and the Francis Delafield Hospital, for the single year, 1951. It follows previous reports of end-results in cancer of the cervix from the Columbia-Presbyterian Medical Center, the most recent prior publication being for the years 1939-1943. The 5-year end-results in 368 patients treated for cancer of the cervix during the years 1946-1951 are discussed. These included 118 patients with stage 1, 96 with stage 2, 70 with stage 3, and 19 with stage 4, as well as 32 patients with cancer of the cervical stump and 33 with recurrence of previously treated cancer.

In the 1946-1951 series, 232 patients were treated by radiation and 71 underwent surgery among the 303 patients with primary lesions of the cervix, exclusive of the cervical stump. The relative 5-year cure rate for all primary cases was 42.6%. [The relative 5-year cure rate for the 1939-1943 series, when all the patients were treated by radiation, was 43%.] The 5-year cure rate for stages 1 and 2, when surgery was the primary mode of therapy, was 86.5 and 42.1% respectively. Similar figures for those treated by intracavitary and interstitial radiation were 56 and 44.1% respectively. The 5-year cure rate for patients in stage 2 treated by interstitial implantation of radium was 50%. It was noted that there were somewhat earlier cases in the surgical series, somewhat fewer patients with severe constitutional disease, and a much smaller percentage in whom follow-up examination was incomplete.

The authors conclude that surgical treatment in stage 1 cases yielded a higher 5-year survival rate than did radiation therapy. Various factors, particularly of case selection, made the two series not wholly comparable and leave the question of the absolute superiority of one method of treatment over the other unanswered. The application of radical surgical methods of treatment to 76 (22%) of 335 cases of primary cervical cancer has been associated with a slight, but statistically not significant, improvement in the total cure rate.

The Incidence of Spontaneous Cure of Secondary Amenorrhea and Oligohypomenorrhea. A. Westman. Acta obst. et gynec. scandinav. **37**:261-269 (No. 3) 1958 (In English) [Stockholm].

In order to investigate the incidence of spontaneous cure of secondary amenorrhea and oligomenorrhea, the author studied 2,262 pregnant women, their ages ranging from 19 to 40 years, who were admitted to the antenatal clinic of the Karolinska Sjukhuset in Stockholm during the year 1956-1957. About 60% of these patients had previously been pregnant. The fact that each patient was pregnant was proof-positive of normal ovarian function, i. e., that a previous disturbance, if it had been present, had been cured. Each patient was given a questionnaire in which she was requested to give information about her previous menstrual history. In 173 (7.7%) of these patients there was a history of amenorrhea and/or oligomenorrhea. Of the 173 patients, 85 gave information about the possible causative factors; it appeared that environmental conditions, place of residence or working conditions, and nervous troubles played an important part in those patients in whom the menstrual dis-

turbance had been of short duration. Most of the menstrual disturbances of more than 12 months' duration had come on after childbirth. A critical analysis of these cases has suggested that spontaneous cure occurs in about 80% of the cases, including those in which the duration of the menstrual disturbance has been up to 3 years. According to the literature, hormone therapy is effective in 50% of the cases. However, the value of this treatment appears to have been overestimated; the true percentage of cases in which it results in cure probably is 20%.

Maternal Death Due to Pulmonary Embolism by Amniotic Fluid. F. A. Carone and J.-G. Regueiro Castro. West Virginia M. J. **54**:384-390 (Oct.) 1958 [Charleston].

The case reported is that of a 41-year-old woman, gravida 2, para 1, who was admitted on Jan. 10 at 1:30 p. m., the estimated date of confinement being Jan. 9. When first examined, the patient was thought to be in early labor, with irregular contractions. The fetal head was approximately 2 cm. above the ischial spines, and the cervix was 2 cm. dilated. During the first hour after admission, the labor progressed rapidly and by 3:15 p. m. the cervix was 6 cm. dilated. Demerol was given to ease pain. At 3:30 p. m the patient began to cough and to gasp for air. Within a few seconds she experienced extreme air hunger, stopped breathing, and had a convulsive episode. The blood pressure and pulse were not obtainable. An airway was established, and oxygen was administered. Tracheotomy was begun, but when it became obvious that death had occurred, the operation was not completed. The baby was delivered vaginally with forceps approximately 15 minutes after the mother's death, and, after the usual resuscitative measures, its respiration became established.

On autopsy, significant microscopic lesions were found in the heart, lungs, and uterus of the mother. Foreign material, consisting of squamous cells, mucin, bile pigment, and fat, was found in the pulmonary vessels. Squamous cells, hair, and strands of mucin with clusters of leukocytes were demonstrated in both smears and cell-block preparations of blood from the right heart. The concentration of amniotic particulate matter in right heart blood may have been greater in this case since death occurred in less than 5 minutes, presumably due to massive embolism. Since the particulate constitutents of amniotic fluid have a lower specific gravity then the cellular elements of blood, they settle out as a flocculent layer above the leukocytic cream. Thus, the presence of 3 strata instead of 2 in centrifuged blood from the right heart should be considered pathognomonic for this condition. This procedure may be utilized to establish the diagnosis of amniotic fluid embolism in cases lacking autopsy permission. It is probable that many maternal deaths, without autopsies and labeled thrombotic pulmonary embolism, obstetric shock, or postpartum hemorrhage, actually are fatalities due to amniotic fluid embolism. Some of the deaths which have resulted from amniotic fluid embolism could have been prevented if the proper measures had been instituted. Embolization of the lungs should be considered likely if unexplained cyanosis and shock develop during labor, and oxygen should be administered at once. Papaverine hydrochloride may be given to abolish reflex vascular spasm of the pulmonary vessels and thus prevent pulmonary edema, and atropine or atropine-like agents may be given to abolish cardiac depressor reflexes from the lungs.

When pulmonary edema develops, it should be treated vigorously, and withdrawal of blood may be indicated. Unfortunately, the two measures commonly used to combat shock, i. e., blood transfusion and administration of epinephrine-like compounds, worsen pulmonary edema. Clinical judgment is important in using these agents in patients with amniotic fluid embolism. If death does not occur, attention should be directed to the possible onset of hemorrhagic tendencies because of coagulation defects secondary to infusion of amniotic fluid constituents into the maternal circulation. Incoagulibility of the blood may result and intravascular coagulation may produce hypofibrinogenemia. If this condition exists, it should be corrected by administration of adequate amounts of fibrinogen.

Kyphoscoliosis and Pregnancy. R. Marchand. Laval méd. **26**:309-315 (Oct.) 1958 (In French) [Quebec].

Pregnancy in patients with extensive malformation of the vertebral column usually leads to complications of an unsuspected gravity. Few obstetricians know the danger of cardiopulmonary failure in pregnant women with kyphoscoliosis. The influence of deviations of the spinal column varies greatly according to the seat, form, size, and age at onset of the condition. This study is of patients in whom kyphosis or extensive kyphoscoliosis appeared at an early age. This disease produces a marked vertical compression of the thoracic cage with considerable diminution of the respiratory capacity. The resulting interference with pulmonary circulation brings on hypertrophy of the right heart and later lesions of the myocardium. These patients, who are poor risks for general anesthesia and major surgery, tolerate pregnancy with difficulty. The increase in the volume of the abdomen adds to the intrathoracic compression and restrains the respiratory capacity, which is already diminished by the rigidity of the rib cage. The heart must use more strength to overcome this new resistance and circulatory overloading. Delivery requires a physical effort which may be fatal, especially considering the

fact that kyphoscoliosis is frequently accompanied by abnormalities of the pelvis. These may make natural delivery impossible, and it is often necessary to terminate the pregnancy by cesarean section.

The author discusses the cases of 3 patients. The first, a primipara aged 30 years, had pronounced thoracic kyphoscoliosis which had begun at the age of 11. On admission to the hospital, she had incipient toxemia of pregnancy, edema of the legs, albuminuria of 3 Gm., and a light hypertension of 140/90. The pelvis seemed a little asymetrical and the external diameters slightly diminished, but the upper passage seemed permeable. Labor was artificially induced 2 weeks before term, and natural delivery was seen to be impossible. Five days later a healthy baby was delivered by classic cesarean section. Six days after delivery the patient died of asystole and infection of the right lung. In the second case a woman, aged 38 years, who had had kyphoscoliosis since the age of 4, died of cardiopulmonary failure 13 days after a cesarean section; until then the condition had had no serious consequences. In the third case a woman of 34, with pronounced kyphoscoliosis of the thoracic spine, dyspnea, and rales but whose myocardium was apparently healthy, was treated with digoxin 5 days before surgery. The fetus was premature and cyanosed and died 24 hours after delivery; autopsy revealed pulmonary atelectasis and a hyaline membrane. The mother, who continued to receive cardiac medication several days after delivery, suffered no severe postoperative symptoms.

Pregnant kyphoscoliotic patients should not be treated with medicines and interventions capable of interfering with pulmonary ventilation and the circulation of the blood. The coexistence of a large deformation of the thoracic spine with pregnancy constitutes an immediate danger for the mother and child and poses a difficult problem for the obstetrician, as shown by the deaths of two of these mothers and one of the babies.

Cystadenocarcinoma of the Ovary and Uterine Pregnancy. C. Chávez and P. Chávez. Arch. peruanos pat. y clín. **12**:191-195 (June) 1958 (In Spanish) [Lima, Peru].

Uterine pregnancy which is complicated by either benign or malignant cystadenoma of the ovaries occurs with moderate frequency. According to the literature, the tumor does not interfere with pregnancy, nor does it damage the fetus. Yet the death rate among fetuses in pregnancies associated with ovarian tumors is high (18%). A tripara woman at full term was hospitalized with an enormous abdomen from ascites and with edema from the abdomen to the ankles. A plain roentgenogram of the abdomen confirmed the presence of the fetal skeleton. A diagnosis of polyhydramnios with a living fetus was made. Four days after hospitalization the woman gave birth spontaneously to an infant who was cyanotic and died a few hours after birth. Autopsy showed marked dilatation of the cerebral ventricles, which seemed to have been the cause of death. The mother developed pleurisy during the puerperium, which was controlled by the administration of antibiotics. Two abdominal paracenteses, by which 5,000 and 7,000 cc., respectively, of ascitic fluid were drawn off, were made 2 weeks after parturition. An enormous ovarian tumor was palpated after the paracenteses. The operation consisted of bilateral oophorectomy and removal of the tumor, which was fixed by adhesions to the anterior wall of the abdomen and by a large base to the posterior wall. There were no metastases, but histological study of the tumor showed it to be a cystadenocarcinoma. The postoperative period was uneventful. The patient was given blood transfusions and antibiotics and one week later, after edema had disappeared, was discharged from the hospital. Examination 3 years after the operation has shown that her condition is satisfactory.

Pre-Natal Fetal Electrocardiography. P. Bergman and P. Hall. Acta obst. et gynec. scandinav. **37**:348-357 (No. 3) 1958 (In English) [Stockholm].

The authors report a study on 449 prenatal fetal electrocardiograms obtained from 368 patients in the department of obstetrics and gynecology of the general hospital in Malmö, Sweden. Of the 449 electrocardiograms, 277 (obtained from 239 patients whose pregnancy terminated in normal delivery or legal abortion) were taken during the 15th week of pregnancy or later. Detailed data concerning these 277 electrocardiograms showed that prenatal fetal electrocardiography was useful in investigating obstetric cases in which no fetal heart sounds could be heard and in which there was reason to suspect fetal death. In 6 of 28 such patients the electrocardiogram was positive, i. e., it showed measurable, or immeasurable but nevertheless distinct, potentials in 5 consecutive fetal complexes and therefore objective signs of a living fetus; 4 of these women were later delivered of living infants. The first electrocardiograms obtained from the remaining 2 patients gave a positive result, which was subsequently verified when normal fetal sounds were heard. Electrocardiograms taken on later occasions, however, contained no fetal complexes, and the fetuses which were subsequently delivered of these patients were macerated. Since the electrocardiogram was not always positive even when the fetus was alive, a negative record might be less informative.

Prenatal fetal electrocardiography is also a useful guide in the evaluation of the position of the fetus, but with the technique applied in the present investigation the method proved less satisfactory in the diagnosis of twin pregnancies. The amplitude

of the QRS complex increases during the last 2 months of pregnancy to reach a maximum at term. If pregnancy proceeds beyond the calculated term, this complex seems to decrease in amplitude. It, therefore, appears that prenatal fetal electrocardiography might be useful in the detection of true postmaturity if serial examinations are made.

PEDIATRICS

Bacterial Endocarditis in Children with Heart Disease. J. G. Cutler, P. A. Ongley, H. Shwachman and others. Pediatrics **22**:706-714 (Oct., Part 1) 1958 [Springfield, Ill.].

The authors report on 12 boys and 12 girls, between the ages of 8 months and 16 years, with bacterial endocarditis and with preexisting congenital or rheumatic heart disease, who were admitted to the Children's Hospital and the House of the Good Samaritan in Boston between 1944 and 1956. In the group of 6 patients with congenital heart disease of cyanotic type, bacterial endocarditis occurred most commonly in those with tetralogy of Fallot, since 5 of the 6 patients had this congenital defect. In the group of 9 patients with congenital heart disease of acyanotic type, there was a slight predominance of those with ventricular septal defect and coarctation of the aorta. In the group of 9 patients with rheumatic heart disease, mitral insufficiency was the predominant lesion.

The duration of symptoms attributable to bacterial endocarditis before admission to hospital varied from 5 days to 9 months. Twenty-two of the 24 patients were admitted with a history of fever, which subsided when therapy was instituted. Anorexia with associated weight loss was present in 20 patients. Joint pains occurred in 9 patients, and clubbing in 10. Murmurs were noted in all patients. Twenty patients had cardiac hypertrophy, which was progressive since the onset of endocarditis in 10 patients with congestive heart failure. In 12 patients embolism occurred, most frequently in the lungs or brain. Petechiae were observed in 12 patients. Enlargement of the liver was present in 8 patients, and enlargement of the spleen in 16. There was poor dental hygiene with multiple caries in 11 patients. The causative relationship between this physical finding and bacterial endocarditis warrants repeated emphasis. A significant anemia of either normochromic or hypochromic type was present in 19 patients.

Alpha-hemolytic streptococci were isolated from 13 patients, including 7 of the 15 with congenital heart disease and 6 of the 8 with rheumatic heart disease. Three of these 13 patients died. In 2 patients, 1 of whom died, Staphylococcus pyogenes var. aureus was the offending agent. Pneumococci, beta and gamma streptococci, hemophilus parainfluenzae, and Pseudomonas organisms were detected in the remaining patients. Twenty patients (83%) recovered from the acute illness. Antibiotics were used in 23 of the 24 patients. Aqueous salts of penicillin were considered to be the drugs of choice in the treatment of all streptococcic infections. Because of the gravity of the infection, a minimum duration of 3½ weeks of treatment was adhered to. The parenteral route of administration seemed to assure more predictable and uniform concentrations of penicillin in the blood than the oral route. The measure of in vitro sensitivity of the offending organism was used as a guide in the selection of antibiotic agents in nonstreptococcic infections. The prognosis depends on the interval between the onset of illness and the institution of therapy, the sensitivity of the infecting organism to the antibiotics used, adequate dosage of the antibiotics, the severity of the underlying heart disease, and the development of complicating factors, such as congestive heart failure or embolism in vital organs, which are bad prognostic signs despite effective antibiotic therapy.

Salmonellosis in a Premature Nursery Unaccompanied by Diarrheal Disease. J. Watt, M. E. Wegman, O. W. Brown and others. Pediatrics **22**:689-705 (Oct., Part 1) 1958 [Springfield, Ill.].

The authors report on an epidemic of salmonellosis which occurred in the premature unit of the Charity Hospital of Louisiana in New Orleans. The introduction into this large nursery of 6 apparently healthy premature infants, who were later found to be infected with Salmonella tennessee, led to an epidemic spread of the infection over a 4-month period. None of the 6 infants whose initial rectal swabs yielded Sal. tennessee, a potential pathogen, and none of the 28 additional infants whose cultures became positive after initial spread of the Salmonella infection in this nursery had taken place were clinically ill at any time. Of 130 positive Salmonella cultures which were obtained from the 34 infants, 104 (80%) were found to be positive without the aid of enrichment technique. Six of the 34 infants known to have been excreting Sal. tennessee would have escaped detection if enrichment mediums had not been used.

The original source of the infection could not be determined. Feedings, contact with other patients, and infected animals could be eliminated as modes of spread. Rectal-swab cultures of nurses and attendants were all negative. Infection of air was revealed by obtaining Sal. tennessee from one of 30 swab samples taken of air-conditioning filters. Positive Salmonella cultures were obtained from bedside tables and recently changed cribs. A positive culture was obtained from the hands of one nurse immediately after washing. Evidence was found that increase in the spread of the infection was associated with decrease in amount of nursing

care. It is inferred that defective nursing techniques, particularly hand washing, were the chief mode of spread. This outbreak was unique in that an identifiable member of a frequently pathogenic group caused infection but not illness. In similar outbreaks, thorough hand washing should be emphasized as an important and efficient barrier between infected and noninfected infants.

Contribution to the Study of the Incidence of Morbidity and of Disorders Secondary to Serofibrinous Pleurisy in the Course of Pulmonary Tuberculosis in Children in the Period Before and After the Advent of Antibiotics. F. Batini and F. Biondi. Gior. clin. med. 39:1123-1143 (July) 1958 (In Italian) [Bologna, Italy].

The authors review the incidence of morbidity and of disorders secondary to serofibrinous pleurisy among 7,312 hospitalized children, aged 2 to 15 years, with pulmonary tuberculosis in the period before (1933-1948) and after the advent of antibiotics and other anti-infectives (1949-1956). Serofibrinous pleurisy developed in 292 children, one-half of whom had the disease on admission; in the other half it developed during the hospitalization period. The incidence of serofibrinous pleurisy was higher among boys (157) than among girls (135). The patients were followed up for 9 months after the remission of serofibrinous pleurisy for possible development of disorders secondary to this disease.

During the period preceding the use of anti-infectives (1933-1948), 207 children had serofibrinous pleurisy, and 174 (84%) recovered. The condition of 7 patients remained unchanged, and that of 19 deteriorated; 7 patients died. Disorders secondary to serofibrinous pleurisy developed in 73 children. During the period (1949-1953) when streptomycin and aminosalicylic acid were used in treating 62 patients with serofibrinous pleurisy, 59 (95.2%) were cured, but the condition of 3 became worse. Disorders secondary to serofibrinous pleurisy developed in 5 patients. During the period (1954-1956) when isoniazid was used in treating 23 patients with serofibrinous pleurisy, all the patients were cured, and disorders secondary to this disease developed in only 1.

The incidence of serofibrinous pleurisy as a complication which developed during the hospitalization of children with pulmonary tuberculosis decreased considerably on the advent of antibiotics and, in particular, after the introduction of the antibacterial agent, isoniazid. However, the occurrence of this form of pleurisy as an accompaniment to tuberculous disease on admission in this group of children remained unchanged in terms of percentage, but the age at incidence was raised, on an average, from 11 to 15 years. The authors suggest prolonged maintenance therapy with anti-infectives in children who have recovered from serofibrinous pleurisy as a form of chemotherapeutic prophylaxis for the prevention of disorders secondary to this disease.

Acute Poisoning Associated with Inhalation of Mercury Vapor: Report of Four Cases. F. T. Matthes, R. Kirschner, M. D. Yow and J. C. Brennan. Pediatrics 22:675-688 (Oct., Part 1) 1958 [Springfield, Ill.].

The authors report on 4 members of a Negro family, a 19-year-old mother and 3 children, aged 30, 20, and 4 months, respectively, who were brought to Jefferson Davis Hospital in Houston, Texas, about 36 hours after exposure to mercury vapor. The mother had painted a small gas space-heater with a mixture of mercury, turpentine, and aluminum paint and had heated the stove in an attempt to make the mixture adhere to the surface. The heater was allowed to burn all night while the mother and children were asleep in their 2-room home. The 20-month-old infant was dead on admission to hospital, and the other 2 infants died 66 hours and 5 days, respectively, after the onset of symptoms. The mother was acutely ill for 48 hours after her admission, and thereafter there was steady improvement. The illness of all 4 patients was characterized by the sudden onset of tachypnea, cough, fever, gastrointestinal disturbances, and central nervous system manifestations. Ordinary laboratory tests were not helpful in establishing the diagnosis. Quantitative analysis of the urine for mercury was suggestive but not diagnostic. Chest roentgenograms revealed interstitial pneumonitis. Autopsies were performed on the 3 children, and analysis of tissue for mercury in the lungs, liver, and spleen of 2 showed substantially increased mercury content. The outstanding pathological features in the 3 children were erosive bronchitis and bronchiolitis, with severe interstitial pneumonitis.

At the present time the most generally accepted therapy for acute poisoning caused by ingestion of mercury consists of early administration of dimercaprol (BAL). Its use is probably also indicated in acute poisoning caused by inhalation of mercury vapor. Supportive care in the form of oxygen, mist, and parenterally administered fluids is indicated.

The Treatment of Acute Respiratory Infection in Infants. H. I. A. Nisbet and F. Wilson. Brit. J. Anaesth. 30:419-434 (Sept.) 1958 [Altrincham, England].

In spite of modern advances in treatment, there is still a significant rate of mortality among infants who suffer from acute respiratory infections. Failure to clear secretions from the air passages results in severe respiratory obstruction and increasing hypoxia. Oxygen demand is increased by virtue

of the increased respiratory effort, while oxygen supply is diminished because of the defective ventilation. When such a state of respiratory insufficiency exists, antibiotics are of little value unless the airway can be maintained until such time as they can exert their beneficial effect. Similarly, an obstructed airway must reduce the value of oxygen therapy. Methods by which this state of respiratory insufficiency may be alleviated are discussed. These include the use of endotracheal intubation, suction, bronchoscopy, tracheotomy, posture, and humidity; and of controlled respiration in cases in which the infant is too weak to maintain adequate ventilation by its own unaided efforts.

A series of 18 infants treated by such methods is described. Thirteen of these infants survived. Several case histories are presented in some detail, while the others are included in tabular form. The 5 deaths are discussed. In certain of these cases the presence of associated lesions rendered survival unlikely. Some complications are mentioned, in particular those arising from endotracheal intubation in infants. While these problems exist, they should not be held to contraindicate this procedure, especially in cases in which intubation and suction are essential for relief of respiratory obstruction and the reestablishment of adequate ventilation.

Sigmamycin in Pediatrics. J. Felder. Schweiz. med. Wchnschr. **88**:953-958 (Sept. 27) 1958 (In German) [Basel, Switzerland].

Signemycin (Sigmamycin) is a combination of 2 parts of tetracycline and 1 part of oleandomycin. This combination drug was available for oral application in the form of capsules and of a sirup, and for intravenous and local application in the form of ampuls. The author reviews his experiences with it during a 6 months' treatment of 128 children, in 110 of whom the therapeutic result could be verified by clinical and bacteriological data. This group included children with septicemia, purulent meningitis, infections of the respiratory tract, osteomyelitis, arthritis, enteritis, infections of the urinary tract, purulent skin diseases, and suppurative lymphadenitis. A table shows that signemycin produced cure in 115 of the 128 children and failed in only 6. The therapeutic effect appeared promptly, and the drug was well tolerated. Secondary effects of the drug were observed in about one-fifth of the patients, but they were harmless, requiring premature interruption of the treatment in only one patient.

All strains of staphylococci that were tested were sensitive to signemycin. The reliable and prompt action of the drug and the fact that it can be administered by various routes and that it is well tolerated make signemycin one of the most useful therapeutic agents against serious bacterial infections caused by many different micro-organisms. In very acute cases, especially in septicemia, purulent meningitis, arthritis, osteomyelitis, and complicated pneumonia, the author recommends a high initial dosage, orally of 100 to 200 mg. per kilogram of body weight daily, or intravenously of 50 mg. per kilogram daily.

DERMATOLOGY

Effect of Oral Steroid on Non-Inflammatory Scalp Ringworm. N. M. Kanof. J. Invest. Dermat. **31**:139 (Sept.) 1958 [Baltimore].

A 9-year-old Negro boy was seen at Children's Hospital, Washington, D. C., for alopecia areata of 2 years' duration. The child also had noninflammatory ringworm infection of the scalp with typical fluorescence of broken-off hairs on examination with Wood's light. After 2 weeks of oral therapy with prednisone (Meticorten), 5 mg. 4 times daily, for alopecia areata and of local therapy with diamthazol (Asterol) dihydrochloride ointment for the ringworm, there was a definite lessening of the number of fluorescent hairs in the ringworm sites. The application of Asterol ointment was then discontinued, and the patient was given only steroid therapy orally. At the end of 6 weeks there was no evidence of fluorescence under the Wood light. The alopecia areata was greatly improved.

Subsequently, a small pilot experiment was carried out on 8 children with noninflammatory tinea capitis due to Microsporum canis. All these patients had involvement of at least two-thirds of the scalp and had been refractory to topical therapy. After 4 to 10 weeks of oral therapy with prednisone, 20-25 mg. daily, all the patients demonstrated a marked change in the affected scalp hairs—either in a marked decrease in the number of broken-off fluorescent hairs or in a peculiar change of the fluorescence from brilliant emerald green to a grayish-white hue. It was especially interesting to note that, wherever fluorescence could no longer be observed, hairs of normal length were present. Further observations are required to confirm and to interpret these effects.

A New Oral Antipruritic. P. L. Williams. Northwest Med. **57**:1162-1164 (Sept.) 1958 [Seattle].

This report is concerned with trimeprazine (Temaril), which is the tartrate salt of *dl*-10-(3-dimethylamino-2-methylpropyl)-phenothiazine. Since preliminary investigations with trimeprazine had indicated that this drug, when taken orally, exerts a potent and seemingly specific antipruritic effect in such unrelated conditions as biliary cirrhosis, poison ivy, and neurodermatitis, it seemed worthwhile to undertake an evaluation of trimeprazine in a private dermatological practice to elucidate its antipruritic effect.

Ninety patients, in whom severe pruritus was a distressing and complicating factor in acute and chronic dermatoses and systemic diseases, were treated with trimeprazine in the course of the past year. The patients selected were chiefly those in whom pruritus had been completely or partially refractory to other forms of therapy, such as topical applications or systemic administrations of steroids, antihistamines, sedatives, and tranquilizers. They ranged in age from 1 year to 75 years; 68 were female, and 22 were male. All but 2 were ambulatory. The initial dose consisted of one 2.5-mg. tablet taken 2 or 3 times a day. As the study progressed, it was evident that drowsiness, a mild side-effect, could be largely eliminated by having the patients take their dose of trimeprazine just prior to meals. The dose taken before retiring was usually twice the daytime dose because of increased nighttime itching. Even though nighttime doses were sometimes as high as 20 mg., lethargic effects the following morning were reported by only one patient. The author concludes that trimeprazine is an effective antipruritic when given orally and that it can be administered in small daily doses. It produces no serious untoward effects, even upon prolonged administration, and permits a reduction in concomitant therapy.

The Nylon Brush. A. Savill. Brit. J. Dermat. **70**:296-299 (Aug.-Sept.) 1958 [London].

The author comments on the histories of several patients who complained of hairfall which ceased when a nylon brush was replaced by a bristle brush. Several persons on being questioned admitted that, when brushing with a nylon brush, more hair came out than when brushing with a bristle brush. In the use of nylon brushes some hairs appear to be pulled out with roots intact. The old-fashioned hair brush is becoming rare, since its bristles, taken from hogs and wild boars of Siberia and the coldest regions of Manchuria, are now difficult to obtain. The need to produce another type of brush resulted in the nylon brush. The bristles of this brush are composed of monofilaments of synthetic nylon, which are cut to the required length; this process can leave an uneven square end, which is injurious.

In studying various types of nylon brushes under a magnifying glass, the author found that nylon bristles have different types of points: (1) rounded points, like the head of a match—safe to use; (2) square points, which look as if cut square—not safe; and (3) square-cut ends, gently rounded off—not so harmful. Furthermore, some firms are replacing nylon bristles with molded Polythene quills which are smooth and resilient, with rounded ends. This kind of brush ensures that the hair shafts do not become entangled, frayed, or pulled out by the roots.

UROLOGY

Treatment of Carcinoma of the Bladder. J. C. Anderson. Brit. J. Urol. **30**:330-337 (Sept.) 1958 [Edinburgh].

Although bimanual pelvic examination may help by proving or excluding the presence of gross invasion of the pelvic cellular tissues, or microscopic examination of fragments obtained by various means may yield some information regarding the character or activity of the tumor, the cystoscopic appearance is the most certain guide to treatment of bladder carcinoma, and it is of paramount importance that the surgeon and radiotherapist should cooperate. The author seldom uses general anesthesia for cystoscopy but generally only a local anesthetic. For the induction of deeper anesthesia he uses a caudal or sacral, but never a spinal, anesthetic. Some information is gained as the cystoscope is passed; it may impinge on a growth or be deflected. The patient empties his bladder before he comes for examination, and residual urine is noted. The ease with which the bladder is washed clear and its capacity are informative. The cystoscopic appearance of the tumor determines the choice of treatment, although the age and physical condition of the patient and the infection may influence it to some extent.

The choice is governed by the desire to keep the ureters in the bladder as long as possible. If the villi are fine and the base narrow, with no surrounding epithelial change, varicosity, or sign of lymphatic obstruction, cystoscopic diathermy is employed, even if the lesions are multiple. Suction or transurethral resection may help to reduce the size of a large tumor. If the lesions are recurrent or multiple, the posterior part of the urethra is examined for seedlings. If the tumor is too large for accurate assessment, open operation may be advisable. The author decides upon an open operation (1) when the tumor has blunted fronts, has a wider base, is sessile, or if there are varicosities or a velvety creep from the base; also when there are satellites close to it or other local or diffuse epithelial changes and (2) if the tumor is solid, nodular, or invasive, is less than 3 or 4 cm. in diameter on the base of the bladder or 5 cm. in diameter elsewhere, and has not invaded the pelvic cellular tissues. Bullae appear when the growth invades the bladder wall; the bullous edema is gross, and the bladder becomes fixed when the growth invades the pelvic cellular tissues.

If the diameter of the growth is more than 4 cm. and it has invaded the extravesical tissues, then supervoltage roentgen-ray irradiation is the treatment of choice. Multiple papillomas should be kept under control by cystoscopic diathermy for as long as possible. When this is impossible, a choice must be made between wide partial cystectomy, supervoltage roentgen-ray irradiation, or, when these

have failed, total cystectomy, always remembering that the posterior part of the urethra may be involved as well as the bladder. After cystectomy it is better to create an ileal bladder, because the ureters are divided and anastomosed at a higher level where their blood supply is better. One type of bladder carcinoma difficult to diagnose resembles eczema and is accompanied by intense dysuria. The appearance is explained by rapid intramural spread. The prognosis is bad unless supervoltage roentgen-ray irradiation is given early. A dose of 5,000 or 6,000 r is aimed at. The results of treatment by supervoltage irradiation are miraculous, particularly in the solid infiltrating carcinoma which may vanish, leaving an apparently healthy mucosa. If it does not disappear completely, it may shrink; if ulcerated, it may heal; and, as a rule, it stops bleeding. The patient may be free from pain and discomfort for several years, perhaps until he dies of some other condition. After a lapse of time the growth may come to life again, but cystectomy or ureteric transplant can still be done.

The Investigation and Significance of Persistent and Recurrent Urinary Infection in Children. W. I. Forsythe and I. R. Wallace. Brit. J. Urol. **30**:297-302 (Sept.) 1958 [Edinburgh].

In children with persistent or recurrent urinary infection, it is important to use all available diagnostic procedures in order to discover the true nature of the malady before irreparable damage is done to the urinary system. The authors present observations on 17 boys and 34 girls who were investigated because of persistent and recurrent urinary infection. Except for 3 boys who were 18 months (2) and 2 years old, respectively, the ages of the 51 children ranged from 4 to 14 years. Eight boys and 11 girls had persistent urinary infection, and 9 boys and 23 girls had recurrent urinary infection. Of the 19 children with persistent infection, 5 boys and 6 girls showed abnormalities. Of the 32 children with recurrent infection, 9 boys and 13 girls showed abnormalities. A critical analysis of the symptoms did not show any significant difference between the patients with abnormalities and those without. The clinical examination was of little value because, apart from 2 children with palpable bladders, no abnormal physical signs relevant to the genitourinary tract were found. In 20 children the infecting organism was Escherichia coli, and in the remainder a variety of organisms was found. Intravenous pyelography revealed abnormalities in 18 cases, but the true nature of these was not appreciated in 9 cases until micturition cystography was undertaken, and in 4 cases retrograde pyelography was needed before the exact nature of the abnormality was discovered. Micturition cystograms revealed abnormalities in 26 cases, but the full nature of these was not appreciated in 9 cases until intravenous pyelography was undertaken, and in 2 cases retrograde pyelography was needed before the exact nature of the abnormality was discovered. Thus, in 28 cases intravenous pyelography and micturition cystography were sufficient to establish the complete diagnosis, and in only 5 cases was retrograde pyelography required.

The authors advise excretory urography and micturition cystography in the initial investigation of these children. If this procedure is followed, many children will avoid unnecessary instrumentation. Should the findings prove inconclusive, though, urethroscopy, cystoscopy, and retrograde pyelography must be undertaken. Observations on boys revealed that 67% of those with recurrent and 63% of those with persistent urinary infections had lesions causing obstruction or stasis. Of 19 girls with anomalies, only 1 showed an obstructive lesion; however, abnormal widening of the internal vesical sphincter and vesicoureteral reflux were common in girls. The cause of widening of the internal sphincter is unknown, but an infective origin is unlikely, because the authors found a similar anomaly in 26 girls with enuresis who had sterile urines and no history of urinary infection. A neurogenic cause cannot be excluded, because in many cases it is impossible to distinguish roentgenologically between the inverted spinning-top appearance of the wide bladder neck and the funneling of the vesical outlet in the neurogenic bladder. The authors think that the condition is due to hypotonia of the internal vesical sphincter, but they are unable to say whether or not it is congenital in origin. According to Hinman, urethral ascension to the bladder is a common cause of urinary infection in female infants and girls. An ascending infection is more likely to occur when the internal vesical sphincter is incompetent.

Hunner's Ulcer. C. H. Kinder and R. D. Smith. Brit. J. Urol. **30**:338-343 (Sept.) 1958 [Edinburgh].

The authors review the records of cases classified as Hunner's ulcer at St. Peter's and St. Paul's hospitals in London during the last 10 years. In only 27 of the 42 patients classified as having this condition could Hunner's ulcer be definitely identified. The youngest patient was 33 years old and the oldest 71. No predisposing factor was found, but in 8 women symptoms apparently began after a pelvic operation or childbirth. It is possible that some of these pelvic operations were wrongly performed for symptoms produced by an undiagnosed Hunner's ulcer. There were only 2 male patients, aged 46 and 54 years respectively. The dominant symptoms of Hunner's ulcer were gross frequency, urgency, and pain. The most severely affected patients were confined to their homes because of frequency of micturition occurring as often as every quarter of an hour by day and up to 10 times by night. Pain was both suprapubic and urethral and in some instances was referred to the loin. It was made worse by a full bladder and relieved by micturition.

Physical examination was not helpful. The urine was usually clear apart from occasional hematuria, and any infection was incidental and inconstant. Most patients had had urograms done, and these were always normal apart from showing a contracted bladder in the worst cases. The bladder capacity was often reduced to 4 to 6 oz., rarely as low as 2 oz. Cystoscopy in the conscious patient was painful and the appearances variable. Small hemorrhagic patches were noted in the vault and lateral or posterior walls, which on close inspection often surrounded shallow irregular linear ulcers or trabecular scars. The rest of the bladder was smooth, pale, and parchment-like. The affected areas would heal, only to break down at a later date. The trigone and the fixed part of bladder were never involved. When cystoscopy was carried out with a flushing instrument, petechial spots appeared on the affected areas throughout the bladder. These spots would bleed on further bladder dilatation, and sometimes the mucosa was seen to split.

Conservative therapy, apart from dilatation, was not effective. Ureterosigmoidostomy was performed 10 times, with 2 deaths; the surviving patients obtained complete relief. Ileocystoplasty was carried out 3 times, but its value is difficult to assess. It appears that either the stoma has to be very wide or extensive partial cystectomy has to be performed for relief of symptoms. The differential diagnosis is from tuberculous and other forms of chronic cystitis, and carcinoma of the bladder. Hunner's ulcer is only one form of chronic interstitial cystitis. The etiology is still unknown, but the possible causes are discussed. It is not likely to be infective, but may be due to hormonal influences and may be partly psychosomatic.

Analysis of 200 Cases of Carcinoma of the Prostate Treated Conservatively. E. J. Satter and J. B. Wear. Wisconsin M. J. 57:327-329 (Sept.) 1958 [Madison].

The authors report on 100 patients with carcinoma of the prostate, who were subjected to orchiectomy and treated with Stilbestrol at the University Hospitals in Madison, Wis., during 1941-1942. Results of treatment in this group of patients ("treated group") were compared with those in another group of 100 patients with carcinoma of the prostate who were subjected to transurethral resection only ("untreated group"). The youngest patient in the untreated group was 47 years old and the oldest 87; the average age of this group was 69.9 years. The patient surviving longest in the untreated group lived 9 years, and the patient surviving longest in the treated group lived 15 years. The average life span of the patients in the untreated group was 22 months after establishment of diagnosis; the survival time of the patients in the treated group was 56 months from the time diagnosis was made. The survival time was best in the 70-to-79-year-old patients in the untreated group and in the 60-to-69-year-old patients in the treated group. The 80-to-89-year-old patients in the treated group lived 32 months longer than those in the untreated group. This indicates that age is no contraindication to the institution of orchiectomy and the administration of Stilbestrol for the treatment of carcinoma of the prostate. Eight of the patients in the treated group lived 10 years or longer. Treated patients, 70 to 75 years old, lived half of their normally expected life span, and patients, 75 to 85 years old, lived 75% of their normally expected span. The total of added years of adult life in the treated group, as compared with the untreated group, was 283 years.

OPHTHALMOLOGY

Recovery of Toxoplasma from a Human Eye. M. J. Hogan, P. A. Zweigart and A. Lewis. A. M. A. Arch. Ophth. 60:548-554 (Oct.) 1958 [Chicago].

The authors recovered from the enucleated eye of a 20-year-old man a strain of Toxoplasma organisms which exhibited low virulence for animals. The patient had a quiescent disease up to the age of 12 years. The significance of a chorioretinal scar in the macula of the right eye, which was discovered at the age of 1½ years, was not apparent to the physician or the family. At the age of 12 years the patient had a sudden diminution of vision in his good left eye, which showed a heavy vitreous haze and an indistinct massive yellowish area of inflammation extending from the disk to the temporal periphery. Roentgenograms of the skull showed calcifications. The neutralizing antibody test and the skin test were positive, and a diagnosis of congenital ocular toxoplasmosis was made. Five months after the onset the vitreous haze in the left eye had cleared so that vision was 20/70. Two and one-half years later the lesion was fairly well healed, leaving extensive scarring and pigmentation of the entire temporal fundus. The vision was 20/100. For several years relapses occurred in this eye, so that the vision was lost. The eye became divergent and hypotonic, a cataract developed, and the eye started to shrink. The patient requested enucleation, which was done. The dye-test titer one year after enucleation was 1:16, and the skin test was still positive.

The chorioretinal tissue from the back of the enucleated eye was ground in a mortar, diluted with sodium chloride solution, and inoculated intraperitoneally into 4 mice. The mice did not show signs of illness, and 3 weeks later their brains were removed, ground, and inoculated intraperitoneally into 4 other mice. Six days later these mice showed some signs of illness, and in a small amount of aspirated peritoneal fluid a few organisms were found which strongly resembled those of the Toxoplasma genus. Other mice were given inoculations of this fluid; 8 days later the animals became ill, and extracellular Toxoplasma organisms were found

in their peritoneal fluid. Subinoculations were continued on mice, guinea pigs, and rabbits. The culture studies showed that the Toxoplasma strain originally recovered from the enucleated eye and designated MF strain offered a distinct contrast in virulence to the RH strain isolated and cultured from the eye of an adult by Jacobs and to the strains obtained from persons with severe systemic infections. This finding supports the concept that some cases of inapparent congenital toxoplasmosis, with late exacerbations of the disease, are caused by Toxoplasma strains of low virulence. In many cases of congenital toxoplasmosis the disease is extremely mild and is unrecognized until a late flare-up occurs. The isolation of Toxoplasma organisms from the patient's eye 20 years after birth shows the great persistence of these organisms in pseudocyst form in the tissues, despite the low virulence of the strain.

Ocular Toxoplasmosis: The XIV. Jackson Memorial Lecture. M. J. Hogan. Am. J. Ophth. **46**:467-494 (Oct.) 1958 [Chicago].

According to Hogan, the acute manifestations of congenital toxoplasmosis are well established and include chorioretinitis, encephalomyelitis, and visceral inflammation. Ocular toxoplasmosis may be overlooked in an apparently healthy child until attention is directed to the eyes by the development of a strabismus, by detection of amblyopia in one or both eyes during a routine eye examination, or by the development of increased blurring due to a late relapse of the chorioretinal inflammation. The author reports on 36 children with congenital ocular toxoplasmosis, whose ages ranged between less than 6 months and up to 12 months at the onset of the disease. Seven of the 36 patients showed evidence of cerebral calcification which could be considered to be toxoplasmatic; the condition was unilateral in 11; a late relapse of the congenital infection occurred in 12 patients; and strabismus was the first and most common eye complaint in 20 patients. Nine patients had positive results of dye tests and negative results on skin tests, indicating that the skin test is less reliable for diagnosis than the dye test. Nine patients had dye-test titers in excess of 1:512, and 13 had titers between 1:128 and 1:512. In addition to the 36 patients with congenital toxoplasmosis, there were observed 4 others with a late relapse of congenital toxoplasmatic infections. Toxoplasma organisms were isolated from the enucleated eye of one of these patients 20 years after birth. [The case of the latter patient is reported in detail in the preceding abstract.]

Ocular inflammation rarely occurs during the course of acute postnatally acquired systemic toxoplasmosis, although some cases have been reported. In patients with uveitis, questionable enlarged lymph nodes should be excised for microscopic and cultural studies. The methylene blue tests performed on patients with uveitis in various age groups showed 35% of the serums to be positive in a titer of 1:16 or higher, as compared with a 25% incidence in a miscellaneous group of patients with eye diseases other than uveitis. The correlation of results of the methylene blue test and the toxoplasmin test in 617 patients with uveitis revealed that 198 (32%) had positive results from the dye test and 141 (23%) had positive results from the skin test. Forty-eight per cent of the patients with chorioretinitis reacted positively to the dye test and 36% reacted positively to the skin test. This can be compared with 25% and 18% of the normal population in this area. The various skin tests on 1,241 patients with uveitis and on a miscellaneous group disclosed that about 40% of the patients with chorioretinitis and 18% of the patients with iridocyclitis had positive reactions to toxoplasmin tests. In this same group 43% of those with chorioretinitis and 23% of those with iridocyclitis had positive dye-test titers. The percentage of the incidence of positive dye and skin tests in the iridocyclitis group was the same as in the control group. The cases of 5 adult patients, between the ages of 32 and 53 years, with acquired ocular toxoplasmosis have been reported in detail; 2 of these were associated with acute systemic infections. Treatment with pyrimethamine (Daraprim) and sulfadiazine in patients with acquired ocular toxoplasmosis was found to be disappointing, but further studies seemed to be warranted.

Angiomatosis Retinae, Eleven Years After Diathermy Coagulation. D. Vail. Am. J. Ophth. **46**:525-534 (Oct.) 1958 [Chicago].

The author reports on a 40-year-old woman with angiomatosis retinae (Hippel's disease), who was operated on for a typical angioma in the left eye. The preoperative vision in this eye was 20/70. With the patient under intravenously administered Pentothal sodium anesthesia, the sclera over the site of the lesion between the 3-o'clock and the 4-o'clock position was exposed, and a single ignipuncture was made with a diathermy needle, 1.5 mm. long (40 ma. for 4 seconds). After ophthalmoscopic verification of the accuracy of the first puncture, 7 more ignipunctures were made around it. The scleral area covered was roughly 3 mm. in diameter. Ophthalmoscopic examination showed that the involved area was "cooked," white, and edematous, so that the outline of the cherry-red tumor could barely be seen. There was no intraocular hemorrhage. Recovery was uneventful. A follow-up examination 11 years after the operation showed that the corrected vision in the eye operated on was 20/20. The scar in the fundus of the eye showed slightly more pigmentation. There was no evidence of recurrence of the original angioma or the development of new ones. The cases of 38 patients with angiomatosis retinae treated by electrocoagulation were collected from the literature.

The ages of the patients ranged from 7 to 40 years. Nine of the 38 patients had both eyes operated on. Of the 47 eyes operated on, 33 (70%) were successfully cured, 6 were improved (eyeball saved, poor or little vision), and 8 were complete failures.

Angiomatosis retinae (Hippel's disease) and its systemic counterpart (Lindau's disease) are disease entities now firmly established in medicine. They are probably more common than supposed. Neurologists and neurosurgeons may miss the ocular lesions; ophthalmologists, the systemic ones. Thus, teamwork is essential. Angiomatosis retinae can be divided into 4 stages of progression during its relentless evolution. Stage 1 consists of one or more dilated and tortuous veins, more or less parallel, running usually to the peripheral and precquatorial areas of the retina. They terminate in a circumscribed tumorous area (the angioma) which may be single or, much more rarely, multiple. Stage 2 consists of retinal hemorrhages, but especially of a deposit of flaky lipid exudates scattered in the various layers of the retina. Stage 3 consists of massive exudation and retinal detachment, and stage 4 is terminal with uveitis, absolute glaucoma, and loss of the eye. Of the 47 eyes operated on, the disease was in stage 1 in 10, in stage 2 in 21, and in stage 3 in 9; the stage of the disease was not specified in the remaining 7. Stages 1 and 2 are the most favorable for surgery, although the operation was considered successful in 4 of the 9 eyes operated on early in stage 3. Mild surface diathermy coagulation followed by pinpoint ignipunctures into the tumor itself seems to offer the best prospect for success. If the tumor is destroyed, the feeder vessels shrink in size and lose their tortuosity. The lipid deposits disappear within one year thereafter. If they do not disappear, it presumably means that the tumor has not been destroyed or new ones have developed. The greatest hazard is hemorrhage into the retina, choroid, or vitreous. For this reason diathermy should be applied with the weakest current capable of doing the job and under frequent ophthalmoscopic control. Direct coagulation of the tumor by diathermy or similar agents gives far better and more certain lasting results than those reported to be obtained by roentgen-ray or radium irradiation.

THERAPEUTICS

Pyrimethamine in the Treatment of Polycythemia Vera. J. W. Frost, R. Jones Jr. and U. Jonsson. South. M. J. 51:1260-1265 (Oct.) 1958 [Birmingham, Ala.].

Pyrimethamine (Daraprim) was given to 14 patients with polycythemia vera for periods varying from 3 to 26 months. Three of the 14 patients received 2 courses of the drug, so that a total of 17 courses of treatment were given. The drug was given by mouth in doses of 25 to 100 mg. daily until the red blood cell count fell to normal limits or below. Treatment then was continued with a reduced dose as maintenance therapy in some patients; in other patients administration of pyrimethamine was continued with the same dose and folic acid was given concurrently in order to determine whether the effect of pyrimethamine on the formed elements of the blood could be reversed by folic acid.

In 11 of the 14 patients there was a fall in hemoglobin level, hematocrit, and red blood cell count. The response to the drug occurred slowly over a period of 1 to 5 months. At the same time there was usually relief of symptoms and reduction in the size of the spleen, when this organ was enlarged. In 9 of the 14 patients the disease was controlled by maintenance therapy for periods ranging from 6 to 19 months. In several of the patients side-effects of pyrimethamine were observed. These consisted of thrombocytopenia, leukopenia, atrophic glossitis, ulcers of buccal mucous membranes, alopecia, and megaloblastic bone marrow changes. These side-effects were never serious and could be reversed by folic acid even with continued pyrimethamine administration. The reversal of all demonstrable biological effects of pyrimethamine by concurrent administration of folic acid indicates that its therapeutic effects in polycythemia are entirely due to its function as a folic acid antagonist. Despite some disadvantages, the drug can be used to control polycythemia satisfactorily in most patients.

Meprobamate Idiosyncrasy: Report of a Case and Review of the Literature. N. D. Charkes. A. M. A. Arch. Int. Med. 102:584-593 (Oct.) 1958 [Chicago].

Meprobamate (Miltown or Equanil) has been in use for several years. Reports on toxic effects have been scattered. One death has been reported. This communication presents a case of meprobamate idiosyncrasy, with skin biopsy and skin testing. It reviews the published reports to date and discusses possible etiological factors in the pathogenesis of the anaphylactoid reaction. The records of more than 6,500 patients have been summarized to date. Twenty-three cases of attempted suicide and 113 cases of idiosyncrasy have been reported. In one-third of the 113 cases of idiosyncrasy the reaction began within 8 hours of commencement of drug therapy, and all reactions, except in 2 patients, had occurred by the end of the first week. The earliest response was within 15 minutes. The reaction had not been seen in any suicidal attempt, so that excessive dosage was not a factor in precipitating it.

In meprobamate idiosyncrasy the rash was erythematous, maculopapular, or urticarial, or a combination of these, as in the case reported here, and may resemble a "boiled lobster." Vesicular and pustular eruptions have been noted occasionally. The rash was most prominent in the groins, inner thighs, buttocks, chest, axillas, and antecubital and inframammary folds; fixed eruptions have been

seen. Petechiae were noted in 16% of the cases, almost always nonthrombocytopenic. Ecchymoses were rare, and the only patient with overt bleeding had aplastic anemia. The Rumpel-Leede test of capillary fragility was always positive in cases of purpura. A prominent and often distressing symptom in one-fifth of the cases was pruritus; however, many patients complained only of "burning" or a sensation of warmth. Other symptoms included anorexia, nausea, vomiting, diarrhea, yawning, headaches, chills, and fever, with temperatures of 101 to 103 F (38.33 to 39.44 C). Dizziness, fainting, hypotension, or shock occurred in almost 15%, and a few patients reacted with asthma, ectopic cardiac rhythms, numbness of the legs, emotional upsets, or mental confusion. A prior history of drug or pollen allergy was elicited in only a small number of patients, but, whereas the anaphylactoid reaction rate was only 0.5% for the group of 6,500 as a whole, it was 10 times as great for patients with known allergies.

Some investigators attempted to prove that the reaction was due solely to meprobamate by the administration of one tablet (400 mg.) some time later. This is a dangerous practice and should not be attempted merely to satisfy the curiosity of the clinician. Twenty-eight of the 30 patients who were given another tablet responded with a reaction which was frequently more violent than the original and which in several cases was accompanied by severe shock. At best, this second reaction lasted longer and responded more slowly to steroid therapy than the first. The most important step in the treatment of the anaphylactoid reaction is withdrawal of meprobamate. Indirect evidence is adduced implicating meprobamate as a histamine-liberating agent in certain patients.

Topical Application of a Solution of Pyrazinamide for the Treatment of Tuberculous Empyema. G. Costa and E. Moretti. Minerva med. **49**:3269-3271 (Aug. 29) 1958 (In Italian) [Turin, Italy].

A solution of pyrazinamide was introduced topically twice a week for a period of 70 to 180 days in 18 patients with tuberculous empyema. Pyrazinamide treatment was given concomitantly with collapse therapy to 5 patients and after discontinuance of collapse therapy to 9 patients. Primary spontaneous pneumothorax was present in 2 patients. The first dose of pyrazinamide, consisting of 20 cc. of the solution, was followed by doses of 40 cc. Prednisolone was used as an adjunct to pyrazinamide in treating 3 patients in whom tuberculous empyema developed during collapse therapy. A dose of 100 mg. of isoniazid was combined with pyrazinamide in 6 patients with the chronic type of the disease, who had already been treated with and became refractory to isoniazid. Pyrazinamide brought about disappearance of effusion and made possible reinstitution of an efficacious collapse therapy in 5 patients in whom the disease was present during the artificial pneumothorax. Of 9 patients with tuberculous empyema treated with pyrazinamide after termination of collapse therapy, 4 patients obtained temporary relief for 2 months, 4 patients obtained no benefit, and the effusion turned from purulent into serous in 1 patient. Temporary improvement for 1½ months was observed in one patient with primary spontaneous pneumothorax, and complete healing of the pleural cavity was obtained in one patient.

The best results with pyrazinamide were observed in patients who had not previously received any chemotherapy and in those in whom the disease was of recent date. The combination of pyrazinamide and isoniazid was only slightly efficacious. A mild malaise, chest pain, and fever episodes were the most common side-effects noted at the onset of treatment with pyrazinamide. Five or 6 months after the onset digestive disorders developed in some patients who obtained only temporary relief with the drug. The authors suggest treatment with pyrazinamide in all instances in which benefits from other antibiotics have been exhausted. It may also be used as an adjunct to other antibiotics for the treatment of chronic types of the disease.

Iproniazid (Marsilid) in Angina Pectoris. A. M. Master. Am. Heart J. **56**:570-582 (Oct.) 1958 [St. Louis].

Fifty-eight men and 16 women, between the ages of 40 and 79 years, with typical and severe angina pectoris were treated with iproniazid (Marsilid) for periods ranging from 1 week to 5 months. Each patient was given 50 mg. of the drug 3 times daily after meals. In an attempt to prevent the occurrence of peripheral neuritis and dryness of the mouth, 25 mg. of pyridoxine were given with each dose of iproniazid. Complete relief of pain was obtained by 13 patients and almost complete relief by 28 patients; improvement was doubtful in 4 patients, and 29 were therapeutic failures. Five of the 41 patients who obtained relief and 1 of the 29 patients who did not were in "status anginosus" when the treatment was instituted. Neither the resting electrocardiogram obtained from the patients nor the results of the Master "2-step" test to which they were subjected were altered in the course of the treatment with iproniazid. These findings suggested that the fundamental coronary disease was not altered. The precise mechanism of the relief of pain by iproniazid is unknown. The relief obtained can possibly be explained by cerebral stimulation, with uplift of mood, and increase of the pain threshold. There may be a direct effect on the autonomic nerve connections between the heart and the spinal cord and brain.

Severe side-reactions made withdrawal of the drug necessary in 57 patients. In some patients the drug was tolerated for only one month or less. The

side-effects were mainly gastrointestinal, genitourinary, and cardiovascular; the latter included dizziness, fall in arterial pressure, and syncope. Three patients sustained an attack of acute coronary insufficiency in the course of the treatment, and acute coronary occlusion occurred in 2 additional patients, 1 of whom died. Less common complications were evidences of cerebral stimulation, peripheral neuritis, dryness of the mouth, hepatitis, and significant gain in weight. The fall in blood pressure is probably a factor in syncope and in attacks of acute coronary insufficiency. It may possibly be a factor in the precipitation of coronary occlusion. The physical overactivity associated with euphoria, excitement, and loss of pain may cause coronary insufficiency. For these reasons, the patient receiving iproniazid should be supervised closely. Blood pressure should be measured in the standing position. On the other hand, glyceryl trinitrate (nitroglycerin) should never be taken by the patient except in the sitting or recumbent position. In view of the numerous side-effects, some of which are potentially dangerous, further therapeutic trials with iproniazid should be carried out only in hospitals and by research teams.

Fluoxymesterone Therapy in Advanced Breast Cancer. B. J. Kennedy. New England J. Med. **259:** 673-675 (Oct. 2) 1958 [Boston].

Investigations revealed that the halogenated androgen, 9α-fluoro-11β-hydroxy-17α-methyltestosterone, or fluoxymesterone, is an effective agent in the treatment of advanced breast cancer. It is an androgenic, anabolic hormone that may be administered orally. Fifty-six patients with advanced breast cancer were treated with it over a 2-year period: 48 of these patients had not received previous hormone therapy, and 8 had previously been treated by surgical hypophysectomy. Of the 48 patients, objective regressions of metastatic breast cancer occurred in 18 and subjective improvement in 25. The quality of improvement in the cancer was similar to that previously noted with testosterone propionate. The frequency of objective improvement would appear to be slightly greater than that with testosterone propionate. The obvious smallness of the series demonstrates the need for greater experience to increase the validity of the figure, but it is apparent that patients demonstrating regressions have survived longer than the nonresponding group. Of the 56 patients treated, 27 remain alive.

Observations on the side-effects of fluoxymesterone have revealed masculinizing changes and erythropoietic changes, as noted with other androgenic compounds. In the doses employed, though, the degree of hirsutism and acne has been less than that with testosterone propionate, and the degree of hoarseness, oily skin, and alopecia has been the same as with testosterone propionate. Increase in libido, encountered with testosterone propionate, did not occur with fluoxymesterone. Evidence of hypercalcemia developed in only 7% of the patients after the onset of fluoxymesterone therapy. The ease of administration, the less distressing masculinizing effects, and the antitumor effect attained are such that fluoxymesterone may be considered the androgen of choice in the treatment of advanced breast cancer. Androgenic hormones are most effectively employed in postmenopausal women with osseous metastases. Objective improvement occurs in about 25% of these patients, with a lower rate of response in patients with soft-tissue lesions.

PATHOLOGY

Primary Malignant Melanoma of the Oral Cavity: A Review of 105 Cases. A. P. Chaudhry, A. Hampel and R. J. Gorlin. Cancer **11:**923-928 (Sept.-Oct.) 1958 [Philadelphia].

Primary malignant melanoma of the oral cavity is a rare tumor, the authors having found records of only 105 cases, including 2 previously described by themselves. This review is based chiefly on 93 cases, since the other 12 lacked adequate description. Primary malignant melanoma of the oral cavity occurred nearly twice as frequently in men as in women. This finding is in contrast to that for malignant melanoma of the skin, which affects both sexes equally. The youngest patient in the present study was 22 years of age and the oldest, 90 years; but in nearly 90% of the reported cases the patients were more than 30 years of age, and in 75% more than 40 years, with a peak in the 6th decade. The site of predilection for the disease was the upper jaw, where 75 (80%) of 93 cases originated. The other sites of involvement, in order of frequency, were the lower jaw, cheeks, tongue, and floor of mouth. In nearly 30% of the cases there was melanin pigmentation at the site at which the neoplasm originated. This pigmentation had appeared from a few months to several years before the tumor.

Malignant melanoma of the oral cavity has been reported in all races. In more than half of the 93 cases clinical evidence of lymph node metastases was recorded. In 19 cases there was clinical or roentgenologic evidence of generalized metastases. Of the 61 patients followed, 51 died of the disease. In 24 cases the survival period averaged 18½ months after diagnosis. There were only 3 patients who lived for more than 5 years. The authors feel that, in view of the serious prognosis of the disease, early recognition of the lesion and institution of radical surgery are desirable. The appearance of melanin pigmentation in the mouth and its increase in size and in depth of color should be viewed seriously.

BOOK REVIEWS

Pathophysiology in Surgery. By James D. Hardy, M.S., M.D., F.A.C.S., Professor and Chairman, Department of Surgery and Director of Surgical Research, University of Mississippi Medical Center, Jackson. Cloth. $19. Pp. 704, with 278 illustrations. Williams & Wilkins Company, Mount Royal and Guilford Aves., Baltimore 2, 1958.

This text, on the physiological disturbances observed in patients who are classified as presenting surgical conditions, goes beyond simple surgical patients and includes those presenting diseases for which surgical therapy may not be considered. In a limited space, adequate critical review is impossible. The book begins with a consideration of the physiology of injury and proceeds to fluid balance, surgical nutrition, the physiology of connective tissue, microbiology, burns, cancer, radiation, enzymology, aging, liver and biliary tract, pancreas, blood transfusion, alimentary tract, circulatory system, lungs, anesthesia, endocrine system, nervous system, infancy, and urologic considerations of special interest. In an attempt to emphasize a "surgical slant" some expressions employed might seem far-fetched, such as "surgical enzymology," the heading of one relatively short paragraph; "surgical aspects of aging," which in essence conveys the idea of danger in operating on patients whose vitality is reduced because of age; and the expression "surgical nutrition." It would seem after all that nutrition is nutrition and enzymology is enzymology.

The text is written in a conversational rather than formal style. The author attempts a wide coverage, sometimes exceeding what might appear the limits of the subject as indicated by the title. This may lessen a reader's confidence in what is related, as, for example, his confidence in what one man says in the chapters on the general physiological reaction of the patient to injury, the question of fluid and electrolyte balance, "physiological considerations in cancer," and urologic considerations of special interest. These are separate areas in which much work has recently been done, and a modern text should include sound critical evaluation based on thorough first-hand knowledge. Further perusal reveals some rather important gaps of which the author may not be aware. For example, only one paragraph and one sentence is devoted to the formation of gallstones. No mention is made of the classical studies of Phemister on calcium carbonate stone formation related to intermittent and complete cystic duct obstruction. In the consideration of gastric physiology much attention is paid only to hypersecretion and acidity. The all-important physiologic aspects of achlorhydria receive only one sentence and the word "achlorhydria" does not even appear in the index. In the discussion on the pancreas clinical reports with important implications for pancreatic physiology are not referred to. For example, the fact that in long-range survivors who had an excision of the duodenum and head of the pancreas with occlusion of the external secretion—this is a different situation than after total pancreatectomy—there may be no appreciable physiological disturbances, and that in human diabetics who had a total pancreatectomy the diabetes is not appreciably if at all aggravated.

Here and there one encounters obvious inaccuracies such as the statement that subtotal gastric resection "first performed by Theodor Billroth in 1881 was based upon the physiologic facts that hydrochloric acid is secreted by the cells of the fundus." Billroth performed a limited pylorectomy for cancer and was never concerned with gastric resection for ulcer since he was ignorant of the acid-ulcer concept. Also this is probably the first occasion where in a physiological treatise reference is made to a fiction "best seller" to help emphasize a point (page 602, "Point of No Return," J. P. Marquand). Probably the best feature of the work is the large number of diagrams, line-drawings, tables, graphs, and photographs. Many appear original and many tell the story without recourse to the text. Here again, however, some questions may arise, as in figure 93, which purports to have settled the question about the best method for alimentery tract reconstruction after pancreatoduodenectomy. Experienced surgeons would not agree with what is shown. The volume is well bound, the paper of high quality, the type is large, facilitating ease of perusal, and the bibliographies are fairly complete. The work is interesting and would be especially useful for advanced students, interns, residents, and Board examination candidates.

Hearing Therapy for Children. By Alice Streng, M.A., and others. Second edition. Cloth. $6.75. Pp. 353, with illustrations. Grune & Stratton, Inc., 381 Fourth Ave., New York 16; 99 Great Russell St., London, W. C. 1, England, 1958.

This is a somewhat revised edition of the 1955 publication of the same title. It purports "to include for the first time in one book the special skills and knowledge needed by members of those professional groups who work with hearing-handicapped children." Although this is a noteworthy

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purpose, it would be difficult to include in one book all phases of such work and, although presented as a single cohesive work, the book consists of two parts. The first is a general discussion of the problem of deafness in children, causes and treatment of hearing loss, audiometry, and hearing aids. The rest of the book is devoted to specific techniques in the educational management of hard-of-hearing and deaf children. The first part should be helpful as an orientation to the field of pedoaudiology and the second half should be of particular interest and benefit to speech and hearing therapists and teachers of deaf children. The book contains good lists of references, particularly at the end of the chapters dealing with the education of children with impaired hearing. Each chapter has adequate figures and photographs. A few changes could have been made in a second edition which apparently were overlooked; for example, in the chapter on hearing aids, a discussion of the vacuum tube instruments preceded mention of transistor aids, in spite of the fact that practically all hearing aids now dispensed are of this type. The same chapter refers to the approval of hearing aids by the Council on Physical Medicine and Rehabilitation of the American Medical Association, a practice which that body discontinued several years ago. Despite certain shortcomings of this book, most of which may be due to the fact that there are five authors, its value to audiologists and teachers of hearing impaired children is apparent. Less obvious is its value to the general physician or even the otologist.

Circulation: Proceedings of the Harvey Tercentenary Congress Held on June 3rd-June 8th 1957 at the Royal College of Surgeons of England, London. Edited by John McMichael, M.D., F.R.C.P., F.R.S., Professor of Medicine, University of London, London. Cloth, $10.50. Pp. 503, with illustrations. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill.; Blackwell Scientific Publications, Ltd., 24-25 Broad St., Oxford, England; Ryerson Press, 299 Queen St., W., Toronto 2B, Canada, 1958.

The first part of this interesting volume consists of a series of historical essays dealing with the life of William Harvey and related material. These are presented by Kenneth Franklin, Frederick Willius, John F. Fulton, Charles Dodds, Geoffrey Keynes, Tom Hare, and others. The second part deals with a review of present knowledge of the circulation. Space does not permit a complete listing of titles and authors, although this should whet the appetites of all physicians, especially those with special interest in the circulation. To list a few of the participants, they include George Pickering, Louis Katz, Paul Wood, C. Heymans, Gustav Nylin, Donald Gregg, Claude Beck, Andre Cournand, Russell Brock, MacDonald Critchley, Seymour Kety, E. H. Botterell, James Learmouth, Stanley Bradley, and Russell Brain. The broad subjects covered include the role of the heart in circulation, hemodynamics, coronary circulation, pulmonary circulation, results of cardiac surgery, cerebral circulation, splanchnic circulation, and peripheral circulation.

In general the material is well presented although, as with all symposiums, the quality is uneven. There is one profound error of omission in this presentation. While the physiological presentations are complete, the therapeutic aspects discussed are almost entirely surgical. The uninitiated may be led to assume that these distinguished investigators believed that the only substantial progress in the understanding or the treatment of cardiovascular diseases has been by our surgical confreres. In actual fact, the number of patients whose problems are clarified or conditions benefited by the use of digitalis and the many other cardiac drugs, the anticoagulants, and the antihypertensive agents, to mention a few important groups, far exceeds the numbers of patients who will ever come to surgery for their cardiovascular conditions. Therefore, if treatment is considered at all, a more balanced presentation would be desirable. Nevertheless, one cannot but feel that William Harvey would have been pleased that such a distinguished group of scientists was gathered in his honor 300 years after his death and that their words will be available to others throughout the world. This is indeed a test of the durability of one's work.

Ciba Foundation Colloquia on Ageing, Volume 4: Water and Electrolyte Metabolism in Relation to Age and Sex. Editors for Ciba Foundation: G. E. W. Wolstenholme, O.B.E., M.A., M.B., and Maeve O'Connor, B.A. Cloth. $8.50. Pp. 327 with 85 illustrations. Little, Brown & Company, 34 Beacon St., Boston 6; J. & A. Churchill, Ltd., 104 Gloucester Place, Portman Sq., London, W. 1, England, 1958.

This small volume on the relationship of two subjects in the forefront of medical interest, viz., aging and electrolyte metabolism, contains 18 essays with appended discussions by participants in a colloquium sponsored by the Ciba Foundation. Although part of the book deals with electrolyte relationships to age and sex, most of it is concerned with more general aspects of the subject ranging from the genetic control of electrolyte metabolism in the erythrocyte to the effects of severe magnesium deficiency. The participants were eminent authorities in the field whose discussions, based on their own studies, add inestimably to the value of the book. The book should prove of interest to research workers in the field of electrolyte metabolism and its hormonal aspects in relation to age and sex. It is well printed and adequately illustrated, with the more pertinent references to the literature appended to each chapter.

QUESTIONS AND ANSWERS

ADULT IMMUNIZATION SCHEDULES

To the Editor:—*Please suggest optimum intervals for immunization protection of adults against the following diseases (with adequate initial immunization series): smallpox, diphtheria, tetanus, typhoid, influenza, and poliomyelitis.*

Nelson M. Taylor, M.D., Grosse Pointe, Mich.

Answer.—Assuming that adequate initial immunization series have been given to protect against the diseases listed, the optimum intervals for immunization protection of adults are as follows: smallpox, vaccination every three years; diphtheria, immunization not recommended for adults except in cases of Schick-negative reaction in a person exposed to special risks; tetanus, booster dose at the time of each injury where danger of tetanus exists, with reinjection in the absence of an injury at intervals of no longer than five years; typhoid, reinforcing injections every three years; influenza, injection every year for risk cases (as in old or chronically ill persons); and poliomyelitis, not enough time has elapsed yet to learn about the duration of the protection conferred by the Salk vaccine, but a fourth dose, given not earlier than one year after the third dose, could be administered to individuals exposed to special risks. It should be understood that these are general guiding schedules which vary according to the circumstances. For instance, for persons traveling to areas where smallpox is endemic, revaccination at intervals as short as six months may be desirable. The same is true for persons living in typhoid endemic areas, who should get a booster dose every year.

TEST FOR CARBON DIOXIDE COMBINING POWER

To the Editor:—*What is the physiological reason for equilibrating the blood with carbon dioxide in obtaining the value for carbon dioxide combining power?*

M.D., New York.

Answer.—The carbon dioxide combining capacity of blood plasma represents the capacity of the hydroxyl ion in the blood plasma to combine with carbon dioxide, at the usual alveolar air tension of about 40 mm. Hg, to form bicarbonate. Introduced by Van Slyke and Cullen in 1917, this procedure consists in determining the carbon dioxide content of plasma that has been equilibrated with normal alveolar air, which contains about 5 to 6% of carbon dioxide and therefore has a tension of about 40 mm. Hg. From this value, the dissolved carbon dioxide, or carbonic acid, is subtracted, so that the difference represents the bicarbonate content. This type of determination is one measure of the hydroxyl content or "alkaline reserve" of the body. Among the advantages of this procedure is the fact that it does not require collection of blood anaerobically under oil or mercury, as any escape of carbon dioxide from the plasma during centrifuging or standing is counteracted in the actual determination by the equilibration. Among its disadvantages are that equilibration with alveolar air requires additional equipment and is time consuming and laborious; that it does not measure directly the concentration of either bicarbonate or total carbon dioxide in the circulating blood; and, most important, that it does not yield information about those acid-base derangements in which the ratio of bicarbonate ion to dissolved carbon dioxide at the actual carbon dioxide tension, rather than the concentration of bicarbonate ion at 40 mm. Hg, is the determining factor. Consequently, it has become much more common and acceptable to determine the carbon dioxide content of the plasma or serum from blood that has been collected under oil and centrifuged with precautions to prevent loss of carbon dioxide. The relationship between carbon dioxide content, expressed in millimoles per liter, carbon dioxide tension (p), expressed in mm. Hg, and the pH is contained in the well-known Henderson-Hasselbach equation:

$$pH = 6.10 + \log \frac{mM.\ CO_2 - 0.0301\ p}{0.0301\ p}$$

For example, in a case of diabetic acidosis reported in the literature, the carbon dioxide combining capacity was 22.6 vol. % or 10.1 mM. The carbon dioxide content was 5.28 mM. per liter at an actual tension of 11.8 mm. Hg. The pH was, according to the above **equation, 6.10+log** 13.8 or 7.24. The Henderson-Hasselbach equation and determination of carbon dioxide content also permit a readier understanding of other acid-base disturbances. To illustrate, in a case of respiratory overventilation reported in the literature, the carbon dioxide combining capacity of the arterial serum was 40.9 vol. % or 18.4 mM., not clearly abnormal. Yet, the plasma carbon dioxide content was 31 vol. % or 14 mM. per liter, the carbon dioxide tension in the circulation was 14.6 mm. Hg, and the pH was 7.59. In general, the determination of the plasma carbon dioxide content, that is, the sum of the bicarbonate

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ion and the dissolved carbon dioxide at the actual carbon dioxide tension existing in the arterial circulation, may give more distinct and precise clues to the presence of acid-base derangements than the concentration of bicarbonate ion at 40 mm. Hg (the carbon dioxide combining capacity).

"AIR PLATES" AND CONTROL OF HOSPITAL INFECTIONS

To the Editor:—*In an attempt to control staphylococcic infections in the hospital, the administrative and surgical staffs have requested the use of "air plates" throughout the operating room suite. It has been difficult to find much helpful information concerning a standard procedure for collecting such specimens and interpreting the findings. Specifically, what is the optimum time interval for exposure of the plates, how should the total colony counts be determined, and how extensive an attempt should be made to identify the colonies present? Should an attempt be made to identify all the colonies on each plate?*

William D. Kelly, M.D., Elmira, N. Y.

Answer.—The exposure of open Petri plates (blood agar plates or plates containing a comparable good nutrient) at various locations in the operating room has not been standardized. The plates are uncovered at selected locations throughout the room and are allowed to remain exposed to the air for periods ranging from one-half to one hour. On occasion, the plates are exposed in the operating room during different periods of activity and inactivity for comparative information. This procedure may detect bacteria or dust particles which "fall out" and inoculate the medium, and it is more qualitative than quantitative. Bacteria present in air currents are not detected by this method. The slit air sample provides more quantitative results, but the initial cost of the equipment is expensive. A less expensive technique is available in an all-glass impinger apparatus which is reported to be quite satisfactory. With this technique, air is passed through sterile saline solution or broth and quantitative determinations are obtained.

There is no standard of interpretation. The total number of colonies on a plate cannot serve as a true index, since it is only a rough estimate in view of the limitations of the collecting procedure. Laboratory workers should be familiar with the saprophytic forms that might be encountered in the area in question and should be able to differentiate them from potential pathogens, such as staphylococci. Although identification of all colonies obtained in a study of air in an operating room is expensive and laborious, in an epidemic it may be advantageous to make such a specific identification. Air counts may be used more profitably as a device to educate operating-room personnel in the proper techniques to be used in reducing the bacterial counts of the air. Since epidemic strains of staphylococci are carried in the upper respiratory tract of approximately 10% of hospital personnel, it may be more logical to detect epidemic strains in the carriers among the personnel rather than to search for them in cultures made of the air. To investigate the question of identification, phenolphthalein phosphate might be included in the mediums (Barber and others, *J. Path. & Bact.* **63**:57, 1951). This method may be useful if the organism produces coagulase, since this will result in the formation of phosphatase which will split off the phenolphthalein from the phenolphthalein phosphate. Then, if the plate is held over fuming ammonia, the presence of coagulase-positive staphylococci will be shown by a pink color.

The role of the hospital laboratory in a program designed for the control of cross infections within hospitals is an important one. The bacteriologist is often one of the first persons to know of an epidemic situation and can assist in the collection of statistics, check the sterility of supplies, and check the adequacy of sterilization techniques. He is able to store cultures of staphylococci obtained from hospital-acquired infections. These could be of value in the event of an epidemic, since they could aid in determining the specific strain involved in the epidemic and in detecting carriers in the institution.

NEURITIS OF RECURRENT LARYNGEAL NERVE

To the Editor:—*A 55-year-old woman has an idiopathic neuritis involving the left recurrent laryngeal nerve. Every conceivable test has been carried out to determine whether pressure could be exerted on the recurrent laryngeal nerve both in the throat and in the mediastinal region. However, all tests show absolutely negative findings, including tuberculin tests. She has apparently had this condition for two years; this would probably rule out the existence of mediastinal malignancy or a lymphoma. At the present time she is being treated for the resolution of a neuritis of the left recurrent laryngeal nerve. Her chief symptoms are hoarseness and periodic coughing, associated with laryngeal spasm. Surgical exploration of the mediastinal region has been considered. Please give further suggestions. What is the incidence of an idiopathic type of neuritis involving the left recurrent laryngeal nerve?*

S. W. Scorse, M.D., Joplin, Mo.

Answer.—A search for the cause of recurrent laryngeal nerve paralysis can sometimes be unrewarding, and the number of "idiopathic" cases has run as high as 30% in one large reported series. Toxic and inflammatory causes may account for an additional 15-20% of cases. In the situation under

discussion, the duration of the condition would probably rule out the existence of any malignancy. Barium studies of the esophagus and planigrams of the chest and mediastinal areas might be suggested. If there are no findings other than the isolated paralysis, surgical exploration of the mediastinum would not seem justified in view of the above figures. Fortunately, most of the individuals with unilateral vocal cord paralysis of undetermined cause do develop a good voice eventually, and their coughing episodes and laryngospasm disappear. If voice reeducation is hampered by virtue of the position of the paralyzed cord in partial abduction, some type of plastic procedure can be performed to permit contact by the remaining mobile cord.

ANSWER.—There is no entity which can be regarded as idiopathic recurrent laryngeal neuritis. Instances occur in which hoarseness develops for no assignable reason, and it is sometimes the case that nothing can be found to explain the condition, either in local, peripheral, or central nervous system disease. It is possible that in an instance such as this the hoarseness may be the first manifestation of disease involving the vagus nucleus (nucleus ambiguus) in the medulla, due to a local cause or to amyotrophic lateral sclerosis. It is also possible that the symptoms may be the result of involvement of a branch of the posterior-inferior cerebellar artery. If there are no other findings beyond those of hoarseness, only time can determine the cause in the presence of negative findings in the present studies.

SILICA EXPOSURE AFTER TUBERCULOSIS

TO THE EDITOR:—*If it is possible to generalize, should a man who has had pulmonary tuberculosis adequately treated and whose disease has been declared arrested or cured be allowed to return to silica brick yard work where there is even minimal silica exposure hazard? Also, are there any absolute contraindications to prophylactic aluminum dust inhalation—disregarding the question of its value? Special reference is made to coronary artery disease, bronchial asthma, and arrested pulmonary tuberculosis.*

Fred H. McClain Jr., M.D., Mount Union, Pa.

ANSWER.—The answer to the first question would have been an emphatic "no" as recently as 10 years ago. It seems from more recent experience, however, that it is safe to allow workers with adequately treated and inactive tuberculosis to return to jobs where the silica dust hazard has been controlled. By "controlled" is meant that the amount of crystalline-free silica dust in the atmosphere is at all times less than 5 million particles per cubic foot (for particle sizes of less than 10 μ). This must be calculated from the total dust count by knowing the free silica content or percentage of a given dust. Numerous U. S. Public Health Service surveys have shown that a recognizable silicosis will not occur in the working lifetime if the silica dust exposure is kept below that figure. Other studies have shown that silica dust exposure per se does not appear to have a deleterious effect on tuberculosis. Sufficient cellular reaction to the silica to be recognizable by chest x-ray studies must have occurred before the reactivating effect becomes apparent. However, where there is any doubt about the silica dust control, the answer to this question still is "no." When such a worker is returned to a job which has good dust control, it is advisable to continue treatment with tuberculosis drugs indefinitely.

The answer to the second question also must be qualified. There is no evidence that aluminum dust would have a harmful effect on coronary artery disease, but experimental animals with low virulence tuberculosis have shown slight progression of the disease after aluminum inhalation. There have been only rare cases of such progression in humans. As for bronchial asthma, there has been no recorded experience to this consultant's knowledge. If the proponents of the use of prophylactic aluminum dust are correct in their theory that aluminum inhalation tends to relax bronchospasm, then there should be a beneficial rather than harmful effect with bronchial asthma. Proof of this is lacking, however.

SYMPTOMS OF HYPOGLYCEMIA

TO THE EDITOR:—*A thin, 38-year-old man has had spontaneous hypoglycemia since 1951. His blood pressure is 110/72 mm. Hg. Basal metabolic rate is —8% and protein-bound iodine level 5 mcg. per 100 ml. Glucose tolerance findings were as follows: fasting, 110 mg. %; 30 minutes, 60 mg. %; one hour, 60 mg. %; two hours, 58 mg. %; three hours, 64 mg. %; four hours, 68 mg. %; and five hours, 72 mg. %. No sugar was present in the urine. Symptoms of mental confusion, slow mentation, lightheadedness, and negativeness were noted 15 minutes after the glucose tolerance test was begun. These symptoms also occur throughout the day every day and are completely, though temporarily, relieved by ingestion of carbohydrate. One sister has renal glycosuria. A 50-Gm. carbohydrate diet and six feedings per day have not relieved the symptoms. Please suggest further treatment.*

Frank H. Hamilton Jr., M.D., Charlotte, N. C.

ANSWER.—The questioner does not state the method of blood sugar level determination which was used. If this was the Folin-Wu method or one yielding similar results, then the fasting blood sugar value is within normal limits, although it is a trifle higher than the average. Other values are at a level which might give rise to symptoms of hypogly-

cemia in a sensitive individual. If the values were obtained by the Somogyi-Nelson or a comparable procedure, then the fasting value is at the upper limit of normal and consistent with "mild" diabetes. The other values are at levels which ordinarily would not give rise to hypoglycemic symptoms. It would be worth knowing at what time during the period of symptoms (which date back to 1951) the glucose tolerance test was done. Was more than one glucose tolerance test carried out, and, if so, were the results quoted typical of those obtained in other tests? Taking the findings in the glucose tolerance test at their face value, one would be doubtful of the presence of an islet cell tumor. The level after an overnight period of fasting is somewhat above, rather than much below, the average normal, and in the third, fourth, and fifth hours after glucose is given there is a steady, though slight, tendency for the blood sugar level to rise spontaneously. It would appear that in this patient the pancreas is unusually responsive to the stimulating effect of carbohydrate. Certainly a low-carbohydrate, liberal-protein diet is indicated with the amount of fat at that level necessary to maintain proper body weight. It is possible that, with frequent administration of carbohydrate during the day to relieve symptoms, the actual amount of carbohydrate taken in 24 hours is much more than the 50 Gm. stated. No mention is made as to whether hypoglycemic episodes have occurred during the night or in other periods of fasting. Unless these have already been carried out, the following measures are suggested: (1) repetition of the glucose tolerance test; (2) observation of the behavior of the blood sugar level after a prolonged fast, up to 24 hours (this could be done by determining the blood sugar level after an overnight period of fasting, continuing to withhold food, and measuring the blood sugar level every two or three hours until a full 24-hour fast has been accomplished); (3) attempts to relieve hypoglycemic episodes by the ingestion of food predominately protein rather than carbohydrate in content; (4) use of daily medication with belladonna and phenobarbital in appropriate doses; and (5) ruling out causes other than hypoglycemia which might be responsible for the symptoms.

TRANSFIXING LUMBOSACRAL JOINTS

To the Editor:—*What is the current feeling about the use of screws through the zygoapophysial junctions of L-4 and L-5, L-5 and S-1, and S-2 to stabilize the lumbosacral spine?*

C. J. Kilduff, M.D., Lancaster, Pa.

Answer.—The use of screws to transfix the facet joints in the lumbosacral area of the spinal column in conjunction with spinal fusion has been accorded some favor during the past 10 years. Reliable qualified orthopedists have used this method and reported their technique. Adequate follow-up studies, which include the use of other techniques as a control, have not yet been published, so far as is known. Thus, evaluation of the use of screws to stabilize this portion of the spinal column as an adjunct in spinal fusion remains difficult. However, in general, the practice appears to be declining, even among those who advocated it originally. Certain complications have arisen, such as impingement of the transfixing screw on the underlying nerve root as well as the usual complications involved in introduction of a foreign body, such as metal, into bone. At best, the use of screws in this manner would be an adjunct to spinal fusion. The screws cannot fix the spinal column rigidly and would function only as a mechanical aid for bone grafts, placed in one of many ways possible, to become solid.

FOOTBALL FOR FOURTEEN-YEAR-OLD BOYS

To the Editor:—*What is the present consensus on 14-year-old boys playing regular football, as opposed to 6-man football, while they are in high school? Some believe that 11-man football should not be played at all in high schools because of the frequency of epiphysial and joint injuries, since the bones are still growing and since an epiphysial injury may well cause retardation of growth in the involved extremity. The particular boy under consideration is in excellent health but is lighter than the average, weighing about 110 lb. (49.9 kg.). He wants to play in the backfield because of his extreme speed, but it is felt that a fast runner being tackled is more likely to receive injuries than a lineman.*

M.D., New York.

Answer.—If the statistics for particular phases of the game are checked, it will be noted that tackling or being tackled accounts for high incidence of the injuries. Comparison of 11-man and 6-man football as far as injury incidence goes indicates that there are fewer sprains, strains, and bruises in the 6-man game but more fractures and other serious injuries. The 6-man game tends to be more open in nature, but the element of tackling still remains and greater momentum is attained. The boy mentioned in the question is certainly not heavy in comparison to some of the players with whom he might compete in high school. Whether such players are carefully matched in terms of age, height, and weight for their play is important in this framework. There has been much dispute about the hazard to the growth areas of the long bones during adolescence in relation to contact sports, particularly football. Different surveys among orthopedic surgeons have elicited varying replies. While there is no dispute about the hazard, many feel that the supervised situation in high school is safer than the

sandlot activities in which the interested boy may participate if he is excluded from school participation. The question as to whether a 14-year-old boy, presumably a ninth grader, should participate in tackle football involves more than a few issues. A few years ago, Dr. Thomas Shaffer made a study relating to the evaluation of the high school athlete for participation. He feels that maturity is a vital consideration in such an appraisal.

REGIONAL ILEITIS AND PREGNANCY

To the Editor:—*A 24-year-old woman has a history from early childhood of three or four daily bowel movements with mucus but no blood or cramps. One and a half years ago it was noted that she had lost weight, and on examination anemia, elevated sedimentation rate, and a mass about the diameter of a grapefruit in the right lower quadrant were noted. X-ray studies revealed a fistula in the right lower quadrant connecting the rectosigmoid, the cecum, and a loop of distal ileum. A narrow sinus tract about an inch long, ending blindly, and probably originating from the sigmoid was also noted in the left lower quadrant. Two or three small diverticula were also noted in the sigmoid and descending colon. It was noted on fluoroscopy, with barium enema, that the barium entered the cecum and loop of proximal ileum prior to entering the sigmoid. It was noted on upper gastrointestinal studies that barium entered the rectum within one and one-half hours. The diagnosis of regional ileitis with fistula involving the terminal ileum, cecum, rectosigmoid, and a more proximal loop of distal ileum was made, and operation was considered. However, the patient became pregnant at this time with her first baby, and the decision was deferred. She had an uneventful pregnancy, and during her pregnancy and since then she has had no diarrhea except for occasional mild episodes on aggravation. Her weight level, hemoglobin value, and state of well-being are well maintained. A repeated barium enema (done one year after the original studies) showed the same findings, and the mass in the right lower quadrant has remained about the same size. Is it advisable to perform operation with resection at the present time with a view toward avoiding future flare-ups of the disease and further complications, or should the conservative approach of watchful waiting be taken?*

M.D., New York.

Answer.—If the story had ended prior to the patient's pregnancy, operation would have been the treatment of choice—resection of the distal ileum, separation of the fistula from the sigmoid, and removal of the diseased segment of intestine. It appears that, during pregnancy, there has been a good deal of healing of the inflammatory process in and about the ileum and that the patient is now considerably improved from the standpoint both of her general well being and of her weight and her hemoglobin level. However, the presence of the mass indicates that she still has considerable difficulty. Because of the risk at operation and the high incidence of recurrence of ileitis in this type of individual, the conservative approach of "watchful waiting" is entirely justified. However, if further signs of activity in the fistulous tract occur, resection should be reconsidered.

1918 INFLUENZA EPIDEMIC COMPARED TO ASIAN INFLUENZA EPIDEMIC

To the Editor:—*Please give information on the clinical differences between the European type of influenza (epidemic after World War I) and the Asian type. Are there more cases of nervous disorder—spinal, Parkinsonism, or encephalitis lethargica—with the Asian type of influenza than with the European?*

Gottwald Schwarz, M.D., New York.

Answer.—Compared to the A/Swine influenza pandemic of 1918, the A/Asian influenza pandemic resulted in relatively few fatalities. Excess mortality for influenza and pneumonia in the United States was actually less than that for several other influenza epidemics in the decades since 1918. No other pandemic or major epidemic of influenza has been so severe in terms of mortality as that of 1918. Debate still continues as to whether the deaths in 1918 were due primarily to the virus itself or to secondary bacteria. In 1957 and 1958, only a small number of deaths were clearly due to the virus alone. These deaths were caused primarily by severe hemorrhagic tracheobronchitis and/or pneumonia. The majority of the 1957-1958 influenza-associated deaths were caused by complicating bacterial pneumonia. Most nonfatal cases of Asian influenza were not very different from nonfatal influenza cases in 1918. Symptoms in both pandemics were essentially the same. Fever, headache, malaise, myalgia, cough, and sore throat were most often reported. There appear to have been more severe cases of primary viral hemorrhagic tracheobronchitis and pneumonia and more complicating bacterial pneumonias resulting in death in 1918 than in 1957-1958. Whether most deaths were due to the virus itself or to bacteria is uncertain. In both pandemics, small numbers of cases of influenza encephalitis were reported. More appear to have been reported in 1918, but confirmation was not as possible in such cases then as it is now. It is likely that the A/Swine virus caused no more or no less encephalitis than the A/Asian strain. Encephalitis lethargica (Economo's disease) was something quite different and apparently unrelated to A/Swine influenza, although it did become world-wide after the influenza pandemic in the period just before and after 1920.

SALIVARY GLAND TUMOR

To the Editor:—*A small tumor located right at the anterior capsule near the bone was removed, with the facial nerve and some of parotid gland left. Four days after operation the pathologist reported the tumor to be a mucoepidermoid carcinoma in the upper grade of malignancy with a tendency to metastasize. The patient is over 72 years of age. Is surgery indicated? Should the whole parotid gland have been removed and the facial nerve cut? Should x-ray treatment be given?*

M.D., Georgia.

Answer.—Several general principles are applicable when the surgeon is confronted with a swelling or tumor mass of unknown nature in the parotid area. First, he should consider that the tumor is possibly, as it was in this case, carcinomatous. Second, it should be recognized that, in their early stages, some malignant tumors give no clue that they are in fact malignant. The surgery should be designed to encompass the tumor with a surrounding mass of normal salivary gland tissue. If this can be accomplished without injury to the facial nerve it will suffice in many instances. If this was done in the case reported, this consultant would recommend no further treatment at this time. Most salivary gland tumors are moderately radiation-resistant, and it is not advisable to use x-ray therapy as a routine postoperative measure.

DEGENERATION OF THE TEETH

To the Editor:—*Is there any beneficial effect of the combined use of estrogens and androgens for treatment of degeneration of teeth? Mainly, is such treatment as effective as in osteoporosis of senility in the laying down of new bony matrix?*

Murray Russell, M.D., Garden Grove, Calif.

Answer.—It is assumed that "degeneration of teeth" refers to the loss of supporting alveolar bone as is seen in periodontal disease. If this is so, there is no indication in the literature or elsewhere that the use of estrogens and androgens would be of any value in restoring the destroyed supporting bone.

IODINE AND ACNE

To the Editor:—*In a high school health textbook, a footnote says, "Teenagers who have pimples should avoid iodized salt." Is there a medical basis for such a statement?*

Fred H. Wiechman, M.D., Jacksonville, Fla.

Answer.—Most dermatologists agree that there is a medical basis for this statement. Iodine in itself may cause an acneiform eruption. It is recognized that often the ingestion of iodine results in the exacerbation of a preexisting acne vulgaris. This is believed to be due to the excretion of the iodine through the skin with irritation of the pilosebaceous apparatus, a structure which might be termed the "shock-organ" in acne vulgaris. Iodine may enter the system from sources other than iodized salt. Some of the more common ones include fish and sea foods, medication taken internally or applied locally, vegetables grown in a soil with a high iodine content, or drinking water. Many patients' acne gets worse when they move to the sea coast because of the latter source of iodine. Bromine has the same deleterious effect on acne as does iodine, but the other halogens, chlorine and fluorine, do not cause an aggravation of this condition.

TREATMENT OF MILIA

To the Editor:—*An 18-year-old girl has what she thinks is acne. Actually, she has a good many milia (whiteheads) rather than comedones. These were small and primarily over the malar region. In addition, she had a few scaly-appearing seborrheic areas. Her face was rather oily. She had no dandruff particularly. What medicament would be effective in the treatment of these whitish small papules? Incidentally, these are rather firm and do not secrete fluid of any kind. Would dermal abrasion be justified?*

M.D., Alabama.

Answer.—Planing frequently causes the formation of milia itself, so this treatment would not be indicated in this patient. Dermal abrasion does not extend sufficiently deep to remove the adnexa of the skin. Deeper planing may result in scarring that would be more objectionable than the "whiteheads" and more difficult to eradicate. The best treatment for this condition is a tedious one, involving needling of each milium under sterile technique and expressing the contents carefully and completely with a comedone extractor. Treatment of the seborrheic areas with a 3% sulfur precipitate and 3% salicylic acid cream would be indicated also.

RECURRENT INFECTIOUS MONONUCLEOSIS

To the Editor:—*Have there been any reported cases of infectious mononucleosis occurring a second time—not as a recurrence of the initial illness—in the same person? Could infectious mononucleosis be followed or accompanied by infectious hepatitis?*

M.D., Illinois.

Answer.—The degree of immunity conferred by an attack of infectious mononucleosis is undetermined. However, even in communicable diseases known to produce a strong immunity after an attack, occasionally second attacks do occur in certain individuals. The mechanisms of bacterial or viral synergism or interference are not too well known, but the coexistence of two infectious diseases is, in general, a rare event. Liver involvement, with or

without jaundice, occurs in a high proportion of patients with infectious mononucleosis, as shown by abnormal results in liver function tests. The possibility of confusing infectious mononucleosis with infectious hepatitis is especially likely in view of the lymphocytosis which frequently accompanies the latter disease.

ASTHMA AND SEDIMENTATION RATE

To the Editor:—*A patient has an erythrocyte sedimentation rate of 30 mm. per hour. He has had bronchial asthma and some bronchiectasis for several years. As far as can be determined, there is nothing to indicate an infection anywhere. Could the presence of asthma and/or bronchiectasis account for the increased sedimentation rate?*

Clyde K. Walter, M.D., Canfield, Ohio.

Answer.—On the basis of the facts presented, all that can be said is that the erythrocyte sedimentation rate of 30 mm. per hour (assuming that the test was performed by the Westergren technique) could be accounted for by the diseases mentioned, although the moderate elevation may be caused by some other process. Chronic, nonextensive bronchiectasis and asthma as a rule do not cause increases in the sedimentation rate, but during exacerbations the rate frequently increases.

IMMUNOLOGY OF SMALLPOX VACCINATION

To the Editor:—*What is the mechanism of protective action of vaccination against smallpox? Is it a system of antibodies or some other effect of the cowpox vaccine?* *M.D., Illinois.*

Answer.—The relationship between the viruses of smallpox, alastrim, vaccinia, cowpox, and ectromelia is a close one, and a great deal of cross protection, sometimes complete, occurs between them. No difference is detectable between smallpox and alastrim. Vaccinia virus closely resembles smallpox virus, while cowpox virus, on the other hand, is more closely related to the virus of ectromelia. It seems probable that the present strains of vaccinia virus are derived from smallpox rather than from cowpox. The immunological mechanisms of protection are the usual ones, consisting of neutralizing virucidal antibodies and agglutinins, precipitins, and complement-fixing and antihemagglutinating bodies.

CHLOROPHYLLINS

To the Editor:—*Are chlorophyllins harmful in any way?* *M.D., Alabama.*

Answer.—Chlorophyllins are water-soluble derivatives of chlorophyll, the green coloring matter of plants. They are prepared commercially by saponification of a source of chlorophyll, such as alfalfa, and by replacement of the magnesium present in the original chlorophyll molecule by another metal, usually copper, to give a more stable compound. The chlorophyllin used in deodorant preparations and described as potassium sodium copper chlorophyllin apparently is not a pure product. The question has been raised as to whether the copper present in this preparation is a potential source of toxicity. However, the copper in the complex is so firmly bound to the chlorophyll moiety that metallic poisoning would not occur unless an excess of copper were present.

PREGNANCY AND BREAST CARCINOMA

To the Editor:—*Are further pregnancies contraindicated in a woman who has had carcinoma of the breast, duct type, for which radical mastectomy of the left breast and simple mastectomy of the right breast were done?*

R. A. Bussabarger, M.D., Raymond, Wash.

Answer.—There are some surgeons and roentgenologists who believe it is dangerous for a woman who has had an operation for carcinoma of the breast to become pregnant again. The reason for this is that in several instances pregnancy and/or lactation seemed to have induced recurrences. However, this consultant believes that, if this patient remains well for three years without evidence of recurrence or metastases, she may bear more children.

TYPHOID BOOSTER IMMUNIZATIONS

To the Editor:—*How often is an intradermal typhoid-paratyphoid booster dose needed after an initial series of three 0.1-cc. injections at weekly intervals?*

W. M. Foulkes Jr., M.D., Wendell, N. C.

Answer.—An intradermally given booster dose every three years is sufficient under "normal" circumstances. However, persons exposed to heavy risks of infection, i. e., living in areas where typhoid is endemic, should get a booster injection every year.

SMOKING AND VITAMINS

To the Editor:—*What is the effect on vitamin metabolism, especially that of the vitamin B complex group and vitamin C, in the human body in an individual who smokes and inhales 20-40 cigarettes a day?*

W. Forrester Maley, M.D., Chicago.

Answer.—This consultant is unaware of any evidence indicating that cigarette smoking has an adverse effect on the body's ability to utilize vitamins.

JOURNALS ABSTRACTED IN THE CURRENT MEDICAL LITERATURE DEPARTMENT, SEPTEMBER-DECEMBER 1958

Abstracts have been made of important articles in the following journals in the Current Medical Literature Department of THE JOURNAL during the past four months. Any of the journals, except those starred, will be lent by the Library of the American Medical Association to individuals in Continental United States and Canada who subscribe to its scientific periodicals and to members of the American Medical Association and its student organization. No charge is made to members, but the fee for other borrowers is 15 cents in stamps for each periodical. Three journals may be borrowed at a time for a period not exceeding five days. Thus most of these journals are accessible to the general practitioner.

*A. M. A. Archives of Dermatology. Chicago.
*A. M. A. Archives of Internal Medicine. Chicago.
*A. M. A. Archives of Neurology and Psychiatry. Chicago.
*A. M. A. Archives of Ophthalmology. Chicago.
*A. M. A. Archives of Otolaryngology. Chicago.
*A. M. A. Archives of Pathology. Chicago.
*A. M. A. Archives of Surgery. Chicago.
*A. M. A. Journal of Diseases of Children. Chicago.
Acta chirurgica belgica. Brussels.
Acta chirurgica italica. Padova.
Acta chirurgica scandinavica. Stockholm.
Acta clinica belgica. Brussels.
Acta dermato-venerologica. Stockholm.
Acta endocrinologica. Copenhagen.
Acta medica scandinavica. Stockholm.
Acta neurológica latinoamericana. Buenos Aires.
Acta neuropsiquiátrica argentina. Buenos Aires.
Acta obstetricia et gynecologica scandinavica. Stockholm.
Acta pharmacologica et toxicologica. Copenhagen.
Acta radiologica. Stockholm.
Acta tuberculosea scandinavica. Copenhagen.
American Heart Journal. St. Louis.
American Journal of Cardiology. New York.
American Journal of Gastroenterology. New York.
American Journal of Hygiene. Baltimore.
American Journal of the Medical Sciences. Philadelphia.
American Journal of Medicine. New York.
American Journal of Obstetrics and Gynecology. St. Louis.
American Journal of Ophthalmology. Chicago.
American Journal of Pathology. Ann Arbor.
American Journal of Roentgenol. and Radium Therapy. Springfield, Ill.
American Journal of Surgery. New York.
American Journal of Tropical Medicine and Hygiene. Baltimore.
American Review of Tuberculosis. New York.
American Surgeon. Baltimore.
Anales de cirugia Rosario. Argentina.
Anales de la Facultad de medicina de Montevideo. Montevideo.
Anatomical Record. Philadelphia.
Anesthesiology. Philadelphia.
Annali dell' Istituto "Carlo Forlanini." Rome.
Annales medicinae internae Fenniae. Helsinki.
Annals of Internal Medicine. Lancaster, Pa.
Annals of Otology, Rhinology and Laryngology. St. Louis.
Annales paediatrici. Basel.
Annals of Rheumatic Diseases. London.
Annals of Surgery. Philadelphia.
Archiv für Kinderheilkunde. Stuttgart.
Archiv für klinische Chirurgie. Berlin.
Archiv für orthopadische und Unfall-Chirurgie. Munich.
Archives of Disease in Childhood. London.
Archives françaises de pédiatrie. Paris.
Archives des maladies du coeur et des vaisseaux. Paris.
Archives des maladies de l'appareil digestif. Paris.
Archivos argentinos de pediatria. Buenos Aires.
Archivos peruanos de patologia y clinica. Lima.
Archivum chirurgicum neerlandicum. Arnhem.
Arkhiv patologii. Moscow.
Arquivo de patologia. Palhava.
Australian Journal of Experimental Biology and Medical Science. Adelaide.
Australian & New Zealand Journal of Surgery. Melbourne.
Australasian Annals of Medicine. Sydney.
Beitrage zur Klinik der Tuberkulose. Berlin.
Blood. New York.
Boletin de la Asociación médica de Puerto Rico. Santurce.
British Journal of Anaesthesia. Altrincham.
British Journal of Cancer. London.
British Journal of Dermatology. London.
British Journal of Ophthalmology. London.
British Journal of Plastic Surgery. Edinburgh.
British Journal of Surgery. Bristol.
British Journal of Tuberculosis and Diseases of the Chest. London.
British Journal of Urology. Edinburgh.
British Medical Journal. London.
California Medicine. San Francisco.
Canadian Journal of Public Health. Toronto.
Canadian Medical Association Journal. Montreal.
Cancer. Philadelphia.
Cardiologia. Basel.
Chinese Medical Journal. Peking.
Chirurg. Berlin.
Circulation. New York.
Circulation Research. New York.
Cleveland Clinic Quarterly. Cleveland.
Connecticut Medicine. New Haven.
Danish Medical Bulletin. Copenhagen.
Deutsche medizinische Wochenschrift. Stuttgart.
Diabetes. New York.
Die Medizinische. Stuttgart.
Diseases of the Chest. Chicago.
Diseases of the Colon and Rectum. Philadelphia.
Fortschritte auf dem Gebiete der Röntgenstrahlen. Stuttgart.
Gaceta médica de México. Mexico, D. F.
Gastroenterologia. Basel.
Gastroenterology. Baltimore.
Gazzetta medica italiana. Turin.
Geburtshilfe und Frauenheilkunde. Stuttgart.
German Medical Monthly. Stuttgart.
Giornale di clinica medica. Bologna.
Harefuah. Tel-Aviv.
Hawaii Medical Journal. Honolulu.
Illinois Medical Journal. Chicago.
Indian Journal of Medical Sciences. Bombay.
Irish Journal of Medical Science. Dublin.
Jornal brasileiro de neurologia. Rio de Janeiro.
Journal of the American Dietetic Association. Chicago.
Journal of the American Medical Women's Association. New York.
Journal of Bacteriology. Baltimore.
Journal of Bone and Joint Surgery. Boston and London.
Journal of Chronic Diseases. St. Louis.
Journal of Clinical Endocrinology and Metabolism. Springfield, Ill.
Journal français de medecine et chirurgie thoraciques. Paris.
Journal of the Indian Medical Association. Calcutta.
Journal of Infectious Diseases. Chicago.
Journal of International College of Surgeons. Chicago.
Journal of Investigative Dermatology. Baltimore.
Journal of the Kentucky State Medical Association. Louisville.
Journal-Lancet. Minneapolis.
Journal of the Louisiana State Medical Society. New Orleans.
Journal of the Maine Medical Association. Brunswick.
Journal of Medical Society of New Jersey. Trenton.
Journal of Mental Science. London.
Journal of Michigan State Medical Society. St. Paul.
Journal of Neurosurgery. Springfield, Ill.
Journal of Obstetrics and Gynaecology of the British Empire. London.
Journal of Pathology and Bacteriology. Edinburgh.
Journal of Pediatrics. St. Louis.
Journal of the Philippine Medical Association. Manila.
Journal of Tennessee State Medical Association. Nashville.
Journal of Thoracic Surgery. St. Louis.
Journal of Tropical Pediatrics. New Orleans.
Journal of Urology. Baltimore.
Khirurgiya. Moscow.
Klinicheskaya meditsina. Moscow.
Klinische Monatsblätter für Augenheilkunde. Stuttgart.
Lancet. London.
Laryngoscope. St. Louis.
Laval médical. Quebec.
Lyon chirurgical. Paris.
Maandschrift voor kindergeneeskunde. Leyden.
Maryland State Medical Journal. Baltimore.
Medical Journal of Australia. Sydney.
Medicina. Buenos Aires.
Medicina clinica. Barcelona.
Medicine. Baltimore.
Metabolism. New York.
Minerva chirurgica. Turin.
Minerva ginecologica. Turin.
Minerva medica. Turin.
Minerva pediatrica. Turin.
Minnesota Medicine. St. Paul.
Monatsschrift für Kinderheilkunde. Berlin.
Münchener medizinische Wochenschrift. Munich.
Nederlandsch tijdschrift voor geneeskunde. Amsterdam.
Neurology. Minneapolis.
New England Journal of Medicine. Boston.
New York State Journal of Medicine. New York.
Nordisk medicin. Stockholm.
North Carolina Medical Journal. Winston-Salem.
Northwest Medicine. Seattle.
Obstetrics and Gynecology. New York.
Ohio State Medical Journal. Columbus.
Pediatrics. Springfield, Ill.
Pediatriya. Moscow.
Pennsylvania Medical Journal. Harrisburg.
Plastic and Reconstructive Surgery. Baltimore.
Policlinico (sezione pratica). Rome.
Practitioner. London.
La prensa médica argentina. Buenos Aires.
Presse médicale. Paris.
Proceedings of Staff Meetings of Mayo Clinic. Rochester, Minn.
Quarterly Journal of Medicine. Oxford.
Quarterly Journal of Studies on Alcohol. New Haven.
Radiology. Syracuse, N. Y.
Revista da Associacão medica brasileira. São Paulo.
Revista da la Asociación médica argentina. Buenos Aires.
Revista brasileira de medicina. Rio de Janeiro.
Revista Chilena de Pediatria. Santiago.
Revista clinica española. Madrid.

Revista do Hospital das clínicas. São Paulo.
Revista española de pediatría. Saragossa
Revista Médica del Hospital General. Mexico, D. F.
Revue française d'études cliniques et biologiques. Paris.
Revue d'hématologie. Paris.
Revue neurologique. Paris.
Revue de la tuberculose. Paris.
Riforma medica. Naples.
Rivista di clinica pediatrica. Florence.
Schweizerische medizinische Wochenschrift. Basel.
Scottish Medical Journal. Glasgow.
Semaine des hôpitaux de Paris. Paris.
Settimana medica. Florence.
South African Medical Journal. Cape Town.
Southern Medical Journal. Birmingham, Ala.
Surgery. St. Louis.
Surgery, Gynecology and Obstetrics. Chicago.
Terapevticheskiy Arkhiv. Moscow.
Texas State Journal of Medicine. Austin.
Thorax. London.
Tidsskrift for den norske lægeforening. Oslo.
Tuberkulosearzt. Stuttgart.
Ugeskrift for læger. Copenhagen.
United States Armed Forces Medical Journal. Washington, D. C.
Vestnik khirurgii. Moscow-Leningrad.
Virginia Medical Monthly. Richmond.
Western Journal of Surgery, Obstetrics and Gynecology. Portland.
West Virginia Medical Journal. Charleston.
Wisconsin Medical Journal. Madison.
Yale Journal of Biology and Medicine. New Haven.
Zeitschrift für Geburtshilfe und Gynäkologie. Stuttgart.
Zeitschrift für die gesamte innere Medizin. Leipzig.
Zeitschrift für Kinderheilkunde. Berlin.
Zeitschrift für klinische Medizin. Berlin.

*Cannot be lent.

SUBJECT INDEX

The letters used to explain in which department the matter indexed appears are as follows: "E," Editorial; "C," Correspondence; "ab," abstracts; the asterisk (*) indicates an original article in THE JOURNAL.

This is a subject index and one should, therefore, look for the subject word with the following exceptions: Foundations, Lectures, Moving Pictures, and Prizes, under "F," "L," "M," and "P" respectively. "Book Reviews," "Deaths," "Medicolegal Abstracts" and "Societies" are indexed under these titles at the end of the letters "B," "D," "M," and "S." Matter pertaining to the Association is indexed under "American Medical Association." The name of the author, in brackets, follows the subject entry.

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ATP: See Adenosinetriphosphate

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Acad.—Academy	*Indust.—Industrial*
Am.—American	*Inst.—Institute*
A.—Association	*Internat.—International*
Coll.—College	*M.—Medical*
Comm.—Commission	*Med.—Medicine*
Comm.—Committee	*Nat.—National*
Conf.—Conference	*Pharm.—Pharmaceutical*
Cong.—Congress	*Phys.—Physicians*
Dist.—District	*Soc.—Society*
Div.—Division	*Surg.—Surgery*
Found.—Foundation	*Surgs.—Surgeons*
Hosp.—Hospital	*S.—Surgical*

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